A DISSERTATION

ON

UPPER GI ENDOSCOPIC FINDINGS IN PATIENTS WITH BRONCHIAL ASTHMA

Submitted to
THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY
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BRANCH I

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CERTIFICATE

This is to certify that the dissertation entitled **"Upper GI Endoscopic Findings in Patients with Bronchial Asthma"** is a bonafide work done by **Dr. PONNIKRISHNAN.G** in **M.D BRANCH I GENERAL MEDICINE** at Government Mohan Kumaramangalam Medical College, Salem-636030, to be submitted to The Tamil Nadu Dr.M.G.R Medical University, in fulfilment of the University Rules and Regulation for the award of M.D. Degree Branch I General Medicine, under my supervision and guidance, during the academic period from February 2008 to September 2009.

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DECLARATION

I solemnly declare that this dissertation **"Upper GI Endoscopic Findings in Patients with Bronchial Asthma"** was prepared by me at Government Mohan Kumaramangalam Medical College and Hospital, Salem-636030 under the guidance and supervision of **Prof.Dr.R.ANBALAGAN, M.D.,** Professor of General Medicine, Govt. Mohan Kumaramangalam Medical College and Hospital Salem.

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CONTENTS

INTRODUCTION

Bronchial asthma is one of the diseases that are known to mankind for centuries. Asthma could well be considered an epidemic given the number of people involved. According to WHO, more than 150 million people were affected with asthma worldwide resulting in 1,80,000 deaths annually.[1] This figure has increased over the last decade. Although asthma is a global disease, there are important differences in epidemiology, clinical spectrum and management practices.

In India the prevalence of 'asthma' was reported as **2.4%** in a population study on 73,605 individuals conducted simultaneously at four major centres in India with the use of a single definition and uniform methodology employing a validated questionnaire.[2]

The word "Asthma" originates from the Greek word asqma, which stands for "short breaths" or "gasp for breath".Some believe that asthma is a Greek word that is derived from the verb "aazein" , meaning to exhale with open mouth.

The cause of the temporal trends in asthma prevalence is unclear, in part they represent change in diagnostic labeling, but there does not appear to have been a real increase in prevalence. A number of explanations have been proposed, including increased environmental pollution from motor vehicles, urbanization and overcrowding of population, dietary changes associated with affluence and the increased use of bottle feeding with cow's milk in infancy. Increased mortality rates from asthma may also be partly due to changes in

diagnostic labeling, but the widespread use of β-adrenergic agonists has also been implicated.

Much new information on the pathophysiology of asthma has been obtained in the past 15 years, and the recent advent of fibreoptic bronchoscopy as a research tool has allowed detailed examination of the respiratory tract in mild asthma.

It is rightly said that 'all that wheezes is not asthma', but equally all that is asthma need not wheeze.

Despite the scientific approach of the disease, a significant proportion of patients do not have adequate control of the symptoms. This problem puts the physician in a position to probe into the so called **the 'asthma masqueraders'-** diseases that resemble bronchial asthma and other diseases that commonly complicate and aggravate the disease.

Many of the intrathoracic and extrathoracic conditions masquerade and complicate or aggravate bronchial asthma. One among those conditions and is of much curiosity is the **gastro intestinal problem that commonly aggravate asthma - gastrooesophageal reflux disease.**

Though the association of respiratory diseases with the gastro intestinal problems have been known for more than a century, much of attention has been paid for the past three decades only. Prior to 1960's much focus was given on the development of aspiration pneumonia etc by aspiration of gastric secretions as evidenced by the famous **'mendelson's syndrome'**. The association of Bronchial asthma with gastro-oesophageal reflux was given much consideration by the western authors.

Various studies have been conducted to find out the association of the gastro-oesophageal reflux disease with asthma, the mechanisms, and the clinical presentations, diagnostic approach and the therapeutic modalities for prevention and treatment. Much concentration was given in establishing the mechanism of this association.

However, Indian literature regarding the association of the oesophageal dysfunction with asthma are limited.

The latest concept is that ***"acid in the lower oesophagus due to reflux can provoke bronchospasm reflexly via vagus nerve,and this response is more pronounced in patients with bronchial asthma and reflux".*** This reflux theory is well proved beyond doubt as the most accepted one for this association and so any patient who does not respond to routine asthma medications, or having symptoms of gastro-oesophageal reflux should be evaluated for the same.

Among the common investigative modalities available to evaluate the gastro-oesophageal reflux, upper gastro intestinal endoscopy now plays a major role because besides direct visualization it allows tissue sampling. The endosocopic documentation of reflux oesophagitis is more relevant because it indicates sequelae of long standing and moderate to serve reflux disease in most of the occasions.

As there are only limited studies conducted to establish this association we undertook this study to screen the asthmatic patients with **upper gastrointestinal endoscopy and histology** to document the reflux associated changes and other findings in these patients

REVIEW OF LITERATURE

BRONCHIAL ASTHMA

DEFINITIONS

Asthma can be defined as an inflammatory disorder charcacterized by variable airflow obstruction; airway hyperresponsiveness to specific and non specific stimuli; and symptoms of wheezing, chest tightness, cough & occasionally dyspnea.[3] 'Status asthmaticus' or 'acute severe asthma' is defined as a severe episode of asthma unrelieved by usually effective bronchodilator drugs. Refractory asthma is defined as asthma which is difficult to control despite maximal inhaled therapy and some of these patients will require maintenance treatment with oral steroids.[4]

CAUSE OF ASTHMA

Asthma can arise at any age, but there are peaks of onset in childhood and in middle life. Childhood asthma is usually associated with atopic allergy, whereas adult onset asthma often (but not always) arises in non-atopic individuals. Both allergic and non-allergic asthma appear to have significant inherited components. Several lines of evidence suggest that the ability to make large amounts of 1gE which is directed against environmental allergens (atopy) is genetically conferred.[5,6]

It is important to recognize that development of atopy is not sufficient to cause allergic asthma. Nervertheless, atopic allergy is an important inducer of episodic symptoms in those who are already sensitized to airbone allergens. Asthmas arising *de novo* in adulthood is less frequently associated with atopy. Many individuals with later onset asthma appear to develop the condition for

the first time following upper respiratory tract infections. Moreover most individuals with asthma experience acute exacerbations when they develop upper respiratory tract infections.

Occupational asthma is an important cause of ill health in the work place. A wide range of organic and inorganic materials have been implicated as causes of occupational asthma.

BRONCHIAL HYPER-RESPONSIVENESS[7,8,9]

Asthma is characterized by marked variation in the caliber of the intra-pulmonary airways over short periods of time. In addition asthmatic individuals often report acute episodes of asthma on exposure to non-specific irritants such as cold air, inorganic dusts, cigarette smoke, perfumes, paints , pesticides spray etc,. These are not allergic responses, but are exaggerated responses of the airways to the non specific irritants. This phenomenon is termed **non-specific bronchial hyper-responsiveness**. Some agents act directly on the airway smooth muscles (histamine, methacholine, etc) while others act indirectly either by inducing the release of mast cell mediators (adenosine etc) or through neural reflex mechanisms.

Inflammatory events in the Bronchial mucosa

In patients with allergic asthma, exposure to a relevant allergen causes degranulation of mast cells present in the airway lumen and airway mucosa. This leads to the release of histamine and a range of newly formed mediators, which induce bronchoconstriction, oedema, mucus secretion and vasodilatation. Eosinophils are a characteristic feature of asthmatic

inflammation and are capable of causing considerable damage to the bronchial epithelium.

Eosinophils contain several basis proteins (major basic protein, eosinophil cationic protein, eosinophil derived neurotoxin, and eosinophil peroxidase) which induce mast cell degranulation directly. Exposure of autonomic nerve endings beneath and within the epithelium appears to enhance the inflammatory response through the release of the neuropeptides substance P, neurokinin A, and calcitonin-gene-related peptide.

Physiology of asthma:

In the presence of airway inflammation and bronchial irritability, a wide range of insults lead to transient smooth muscle contraction. More prolonged bronchoconstriction and airflow obstruction arise when a chronic inflammatory process is set in train with mucosal oedema, mucus secretion and epithelial damage. These changes in airways caliber affect both large and small airways and lead to an overall increase in airflow resistance. Most of the airways **resistance in health and disease is due to small airways**. Thus it is principally the obstruction of small bronchioles which leads to increased airflow resistance in asthma.The FEV1 and PEFR are decreased and disturbed airflow patterns are clinically audible as wheeze.

Clinical recognition of asthma[10,11]

The cardinal symptom of asthma is generally thought to be wheezing. However a few asthmatics say that they never wheeze, and ,many describe

other airways symptoms such as cough with or without sputum production, chest tightness or simply shortness of breath.

Asthmatic wheezing is polyphonic, and is produced by vibrations set up in small airways that are almost closed off. Just as wheeze signifies narrowing of the airways, so does the sensation of tightness. In asthma, the sensation partly reflects the efforts required to breath and partly arises from the central airways., with those deeper in the lungs being devoid of sensation.

Exertional shortness of breath for the asthmatic has both a variable component, which tallies with the waxing and waning of the airways narrowing and a persistent more fixed component.

Cough is insufficiently emphasized as a symptom of asthma. However, it is one of the commonest symptoms of asthma in children and can be a lone symptom of the condition in adults.

GINA CLASSIFICATION OF ASTHMA SEVERITY BEFORE TREATMENT [12]

Step	Indications
Step 1 Intermittent	Symptoms < once/week Brief Exacerbations Nocturnal symptoms ≤ 2 x/month $FEV_1/PEF \geq 80\%$ PEF/FEV_1 variability < 20%
Step 2 Mild persistent	Symptoms > once/week; < once/day Exacerbations may affect activity/sleep Nocturnal symptoms > 2x/month $FEV_1/PEF \geq 80\%$ PEF/FEV_1 variability 20%-30%
Step 3 Moderate persistent	Symptoms > once/week; < once/day Exacerbations may affect activity/sleep Nocturnal symptoms > 1x/week FEV_1/PEF 60%-80% PEF/FEV_1 variability > 30%
Step 4 Severe Persistent	Symptoms daily Frequent exacerbations Frequent nocturnal symptoms Limitation of physical activities $FEV_1/PEF \geq 60\%$ PEF/FEV_1 variability > 30%

NAEPP Classification of Asthma Severity Before Treatment in Adults and Youths 12 Years and Older [13]

Component of Severity	Intermittent	Persistent		
		Mild	Moderate	Severe
Symptoms	≤2 days/week	> 2 days per week but not daily	Daily	Throughout the day
Night time awakenings	≤2 x/month	3-4x/month	< 1x/week but not nightly	Often 7x /week
Short acting beta-against use for symptoms	≤2 days/week	> 2 days per week but not >1x/day	Daily	Several times per day
interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Pulmonary function	Normal FEV, between exacerbations; FEV_1≥80% predicted, FEV_1/FVC normal	FEV_1<80% predicted; FEV_1/FVC normal	FEV_1<60% but <80% predicted; FEV_1/FVC reduced ≥5%	FEV_1<60% ; FEV_1/FVC reduced >5%
Exacerbations (consider frequency and severity)	0-1 per year		> 2 per year	

ROLE OF PULMONARY FUNCTION TESTS

Pulmonary function tests (PFTs) are essential for diagnosing asthma. In patients with asthma, PFTs demonstrate an obstructive pattern, the hallmark of which is a decrease in expiratory flow rates. Patients experience a reduction in the forced expiratory volume over 1 sec (FEV_1) and a proportionally smaller reduction in the forced vital capacity (FVC). These

reductions produce a decreased FEV_1/FVC ratio (generally <0.70). With mild obstructive disease that involves only the small airways, the FEV_1/FVC ratio may be normal, and the only abnormality may be a decrease in airflow at midlung volumes (forced expiratory flow, 75%). Patients with lung hyperinflation have an increased residual volume and increased residual volume-total lung capacity ratio. The flow-volume loop demonstrates a decreased flow rate for any lung volume and is useful to rule out other causes of dyspnea, such as upper airway obstruction or restrictive lung disease.

The clinical diagnosis of asthma is supported by an obstructive pattern that improves after bronchodilator therapy. Improvement is defined as an increase in $FEV_1$of >12% and 200 cc after 2-3puffs of a short-acting bronchodilator. In patients with chronic, severe asthma with airway remodeling, the airflow obstruction may no longer be completely reversible. In these patients, an alternative method of establishing the maximal degree of airway reversibility is to repeat the spirometry after a course of oral corticosteroids (usually 40 mg/day PO in adults for 10 days).

Lack of demonstrable airway obstruction or reactivity still does not rule out a diagnosis of asthma. In cases in which the spirometry is normal, the diagnosis can be substantiated by showing heightened airway responsiveness to a methacholine or histamine challenge. A chest radiograph should be obtained to eliminate other causes of dyspnea, cough, or wheezing in patients being evaluated for asthma.

NOCTURAL ASTHMA [14,15]

Noctural asthma is an integral part of asthmatic symptomatology. Indeed, it is so characteristic of untreated condition that asthma should not be diagnosed if it is absent. Symptomatically the subject awakes around 3 to 5 am with cough, wheezing or chest tightness. Even if sleep itself is not disturbed, lung function at this time will still be abnormal – ***the morning dip***. Likewise, asthmatic symptoms are more likely to be troublesome on awakening. Improvement follows during the day, so that better lung function and freedom from symptoms are most likely to prevail at 4 pm.

GASTRO OESOPHAGEAL REFLUX DISEASE

GERD is one of the most prevalent gastrointestinal disorders. Population based studies show that **GERD affects 20% of adults,** who report atleast weekly episodes of heart burn, and upto 10% complain of daily symptoms. Reflux is considered 'pathological' when it causes symptoms or complications. 'Reflux' or 'peptic' oesophagitis indicates oesophageal mucosal damage due to the irritant effect of the refluxed gastric contents on the oesophageal squamous mucosa. Oesophagitis is not a prerequisite for the diagnosis of reflux disease; indeed, it is absent in the majority of patients with reflux disease.

PATHOGENESIS:

The pathogenesis of GERD is complex, resulting from an imbalance between defensive factors protecting the esophagus (antireflux barriers, esophageal acid clearance, tissue resistance) and aggressive factors from the stomach (gastric acidity, volume, and duodenal contents).

ANTIREFLUX BARRIERS

It includes the intrinsic LES, diaphragmatic crura, the intra-abdominal location of the LES, the phrenoesophageal ligaments, and the acute angle of His

The LES involves the distal 3 to 4 cm of the esophagus and at rest is **tonically contracted.** It is the major component of the antireflux barrier,

being capable of preventing reflux even when completely displaced from the diaphragmatic crura by a hiatal hernia.

Modulators of Lower Esophageal Sphincter Pressure [16]

	Increase LES Pressure	**Decrease LES Pressure**
Hormones/Peptides	Gastrin	Secretin
	Motilin	Cholecystokinin
	Substance P	Somatostatin
		VIP
Neural agents	α-Adrenergic agonists	α-Adrenergic antagonists
	β-Adrenergic antagonists	β-Adrenergic agonists
	Cholinergic agonists	Cholinergic antagonists
Foods	Protein	Fat
		Chocolate
		Peppermint
Miscellaneous factors	Histamine	Theophylline
	Antacids	Prostaglandins E2 and I2
	Metoclopramide	Serotonin
	Domperidone	Meperidine
	Cisapride	Morphine
	Prostaglandin F2α	Dopamine
		Calcium channel blockers
		Diazepam
		Barbiturates

The oblique entrance of the esophagus into the stomach creates a sharp angle on the greater curve aspect of the gastroesophageal junction, the angle of His.

MECHANISMS OF REFLUX

Transient Lower Esophageal Sphincter Relaxations [17]

Transient LESRs are the **most frequent mechanism for reflux** in patients with healthy sphincter pressures. Transient LESRs occur independently of swallowing, are not accompanied by esophageal peristalsis, persist longer (>10 seconds) than swallow-induced LESRs, and are accompanied by inhibition of the crural diaphragm.Transient LESRs account for nearly all reflux episodes in healthy subjects and 50% to 80% in GERD patients depending on the severity of associated esophagitis .

ESOPHAGEAL ACID CLEARANCE [18]

The second tier against reflux damage is “esophageal acid clearance.” This phenomenon involves two related but separate processes: “volume clearance,” which is the actual removal of the reflux material from the esophagus, and “acid clearance,” which is the restoration of normal esophageal pH following acid exposure through titration with base from saliva and esophageal gland secretions.

SALIVARY AND ESOPHAGEAL GLAND SECRETIONS [19,20,21]

Saliva is the second essential factor required for normal esophageal acid clearance. Compared with gastric acid, saliva is a weak base with a pH of 6.4 to 7.8. Although saliva is ineffective in neutralizing large acid volumes (5 to 10 mL), it easily neutralizes the small amount of acid remaining in the esophagus after several peristaltic contractions.

Modulation of salivation may contribute to GERD. Decreased salivation during sleep is the reason that nocturnal reflux episodes are associated with markedly prolonged acid clearance times.[22] Xerostomia is associated with prolonged esophageal acid exposure and esophagitis. Cigarette smoking promotes GER. Originally attributed to nicotine's effect on lowering LES pressure, cigarette smokers also have prolonged esophageal acid clearance times due to hyposalivation.[23] Finally, the esophagosalivary reflex is impaired in patients with reflux esophagitis and individuals with strictures.This is a vasovagal reflex demonstrated by perfusing acid into the esophagus, which stimulates salivation. This reflex explains the symptoms of waterbrash (copious salivation) observed in some reflux patients.[24]

In addition to saliva, the aqueous bicarbonate-rich secretions of the esophageal submucosal glands dilute and neutralize residual esophageal acid. Acid refluxing into the esophageal lumen stimulates these glands and helps neutralize the acid, even if swallowing does not occur.[25,26]

TISSUE RESISTANCE [27]

Tissue resistance can be subdivided into **pre-epithelial, epithelial, and postepithelial factors**, which act together to minimize mucosal damage from the noxious gastric refluxate. The functional components of tissue resistance include the ability of the esophageal epithelium to buffer and extrude hydrogen ions. Intracellular buffering is accomplished by negatively charged phosphates and proteins, as well as bicarbonate ions.

GASTRIC FACTORS

Gastric factors (volume and ingredients in the gastric refluxate) are potentially important in the production of reflux esophagitis.

GASTRIC ACID SECRETION [28,29]

Acid and activated pepsin are the key ingredients of the gastric refluxate producing esophagitis. Overall, gastric acid secretion is normal in patients with GERD. Local distribution of acid rather than total gastric secretion may be more relevant to the pathogenesis of GERD.

H. pylori infection, especially with the cagA+ virulent strain, is a "biological antisecretory agent" that lowers gastric acidity, thereby possibly protecting from the development of severe esophagitis and Barrett's esophagus.

DUODENOGASTRIC REFLUX [30]

Along with acid and pepsin, duodenal contents may be injurious to the esophageal mucosa. Animal studies demonstrate that conjugated bile acids produce their greatest injury in the presence of acid and pepsin, whereas trypsin and the deconjugated bile acids are damaging in a more neutral environment. These experiments suggest that duodenogastric reflux into the esophagus predisposes to complications of GERD, however, the accurate measurement of duodenogastric reflux is difficult. Traditionally, this phenomenon was defined indirectly by measuring the esophageal pH greater than 7 (i.e., "alkaline reflux").

DELAYED GASTRIC EMPTYING [31]

Recent investigations found only a 6% to 38% incidence of delayed gastric emptying, regardless of the severity of the esophagitis. Delayed gastric emptying is a major factor contributing GERD in some groups such as diabetic patients with autonomic peripheral neuropathy

SYMPTOMS

HEART BURN

The classic symptom of GERD, with patients generally reporting a burning feeling, rising from the stomach or lower chest and radiating toward the neck, throat, and occasionally the back.It occurs postprandially, particularly after large meals or after ingesting spicy foods, citrus products, fats, chocolates, and alcohol. The supine position and bending over may exacerbate heartburn.

ACID REGURGITATION AND DYSPHAGIA

The effortless regurgitation of acidic fluid, especially after meals and worsened by stooping or the supine position, is highly suggestive of GERD.Dysphagia is reported by more than 30% of individuals with GERD. It usually occurs in the setting of long-standing heartburn with slowly progressive dysphagia for solids.

OTHER SYMPTOMS

Water brash, odynophagia, burping, hiccups, nausea, and vomiting. Water brash is the sudden appearance in the mouth of a slightly sour or salty fluid. It is not regurgitated fluid, but rather secretions from the salivary glands in response to acid reflux.

EXTRAESOPHAGEAL MANIFESTATIONS

GER may be the cause of a wide spectrum of conditions including noncardiac chest pain, asthma, posterior laryngitis, chronic cough, recurrent pneumonitis, and even dental erosion. Some of these patients have classic reflux symptoms, but many are “silent refluxers,” contributing to problems in making the diagnosis.

CHEST PAIN

GER-related chest pain may mimic angina pectoris, having a queezing or burning quality; being in a substernal location; and radiating to the back, neck, jaws, or arm. It frequently is worse after meals, can awaken the patient from sleep, and may worsen during emotional stress. Heavy exercise, even treadmill testing, may provoke GER.Reflux-related chest pain may last for minutes to hours, often resolves spontaneously, and may be eased with antacids. The majority of patients with GERD-induced chest pain have heartburn symptoms.

ASTHMA AND OTHER PULMONARY DISEASES [32,33,34]

The prevalence of GERD in asthmatics is estimated between **34% and 89%,** depending on the group of patients studied and how GERD is defined (e.g., symptoms or 24-hour pH monitoring). Symptomatic GERD is an important comorbid condition in asthma patients, being associated with greater asthma severity. **GERD should be considered in asthmatics who present in adulthood, those without an extrinsic (allergic) component, and those not responding to bronchodilators or glucocorticoids**. [Up to 30% of patients with GERD-related asthma have no esophageal complaints. Other pulmonary diseases associated with GERD include aspir-ation pneumonia, interstitial pulmonary fibrosis, chronic bronchitis, bronchiectasis, and possibly cystic fibrosis, neonatal bronchopulmonary dysplasia, and sudden infant death syndrome.

EAR, NOSE, AND THROAT DISEASES [35]

GERD may be associated with a variety of laryngeal symptoms and signs, of which “reflux laryngitis” is the most common. These patients present with hoarseness, globus sensation, frequent throat clearing, recurrent sore throat, and prolonged voice warm-up. Ear, nose, and throat signs attributed to GERD include posterior laryngitis with edema and redness,vocal cord ulcers and granulomas, leukoplakia, and even carcinoma. These changes are usually limited to the posterior third of the vocal cords and interarytenoid areas, both in close proximity to the upper esophageal sphincter.

GERD is the third leading cause of chronic cough (after sinus problems and asthma), accounting for 20% of cases.Dental erosion, the loss of tooth structure by nonbacterial chemical processes, can be caused by GER in healthy subjects and patients with bulimia. Microaspiration of gastric contents is the most likely etiology of these complaints.

Diagnostic Tests for Gastroesophageal Reflux Disease

Tests for Reflux

Intraesophageal pH monitoring
Ambulatory bilirubin monitoring (bile reflux)
Ambulatory impedance and pH monitoring (nonacid reflux)
Barium esophagogram

Tests to Assess Symptoms

Empirical trial of acid suppression
Intraesophageal pH monitoring with symptom analysis

Tests to Assess Esophageal Damage

Endoscopy
Esophageal biopsy
Barium esophagram

Tests to Assess Esophageal Function

Esophageal manometry
Esophageal impedance

ENDOSCOPY

Upper endoscopy is the standard for documenting the presence and extent of esophagitis and excluding other etiologies for the patient's symptoms. However, only **20% to 60% of patients** with abnormal

esophageal reflux by pH testing have esophagitis at endoscopy. Thus, the **sensitivity of endoscopy for GERD is poor, but it has excellent specificity at 90% to 95%.**[36]

The earliest endoscopic signs of acid reflux include edema and erythema, but these findings are nonspecific and vary dependent on the quality of endoscopic visual images.More reliable signs are friability, granularity, and red streaks. Friability (easy bleeding) results from the development of enlarged capillaries near the mucosal surface in response to acid. Red streaks extend upward from the esophageal junction along the ridges of the esophageal folds. Erosions develop with progressive acid injury, characterized by a shallow break in the mucosa with a white or yellow exudate surrounded by erythema. Typically, erosions begin at the esophageal junction, occurring along the tops of mucosal folds where acid injury is most prone, and they may be single or multiple. Erosions can also be caused by nonsteroidal anti-inflammatory drugs, heavy smoking, and infectious esophagitis. Ulcers reflect more severe esophageal damage, being deeper into the mucosa or submucosa and either isolated along a fold or surrounding the esophageal junction. Multiple classification systems for esophagitis have been proposed. .In Europe the most popular scheme is the Savary-Miller classification. The most thoroughly evaluated esophagitis classification is the Los Angeles system, and gaining acceptance in the United States and Europe.[37,38,39]

ENDOSCOPIC GRADING SYSTEMS FOR ESOPHAGITIS

Savary-Miller Classification	
Grade 0	Not applicable
Grade I	Single, erosive, or exudative lesion on 1 longitudinal fold
Grade II	Multiple erosions on more than 1 longitudinal fold
Grade III	Circumferential erosions
Grade IV	Ulcer, stricture, or short esophagus, isolated or associated with grades I-III
Grade V	Barrett's esophagus ± grades I-III
Los Angeles Classification	
Grade A	1 or more mucosal breaks confined to folds, ≤5 mm
Grade B	1 or more mucosal breaks >5mm confined to folds but not continuous between tops of mucosal folds
Grade C	Mucosal breaks continuous between tops of 2 or more mucosal folds but not circumferential
Grade D	Circumferential mucosal break

HETZEL 'S CLASSIFICATION

GRADE	APPEARANCE
0	Normal oesophageal mucosa
1	Mucosal oedema , hyperemia and/or friability of the mucosa
2	Superficial erosions involving <10%of the mucosal surface in the last 5cm of the oesophageal squamous mucosa
3	Superficial erosions / ulcerations involving 10 – 50% of the distal oesophagus
4	Deep peptic ulceration any where in the oesophagus or confluent erosions of >50% of the distal oesophageal squamous mucosa

24- h pH-metry

This is a test to evaluate esophageal acid exposure (measured in terms of pH, mathematical way of measuring amount of acidity or hydrogen ion concentration) and is considered "**gold standard**" for diagnosing GERD. This test is not only used to diagnose GERD but also used to determine the effectiveness of medications used in its treatment in suppressing acid secretion from stomach.

BIOPSY FINDINGS[40]

- Edema and basal hyperplasia (non-specific inflammatory changes)
- Lymphocytic inflammation (non-specific)
- Neutrophilic inflammation (usually due to reflux or *Helicobacter* gastritis)
- Eosinophilic inflammation (usually due to reflux)
- Goblet cell intestinal metaplasia or Barretts esophagus
- Elongation of the papillae
- Thinning of the squamous cell layer
- Dysplasia or pre-cancer
- Carcinoma

NEGATIVE ENDOSCOPIC REFLUX DISEASE (NERD)[41]

- Patients with classic symptoms of GERD and normal esophageal mucosa have been classified as having **endoscopy-negative reflux disease (ENRD), symptomatic GERD, or NERD.** Nonerosive reflux

disease (NERD) is the most common phenotypic presentation of gastroesophageal reflux disease (GERD).

PATHOPHYSIOLOGY

Physiologic studies in NERD patients demonstrated minimal abnormalities when compared to normal subjects. Nonerosive reflux disease patients have a slightly higher rate of failed peristaltic contractions, defined as nontransmitted contractions or contraction waves that do not traverse the entire esophagus. Additionally, NERD patients demonstrate mildly reduced mean lower esophageal sphincter (LES) resting pressure and distal amplitude contractions as compared with normal subjects. Hiatal hernia is a relatively uncommon anatomic finding in NERD patients as compared with patients with erosive esophagitis or Barrett's esophagus. Cameron et al reported that the hiatal hernia prevalence among NERD patients is only 29% as compared to 71% of the erosive esophagitis and up to 96% of the long-segment Barrett's esophagus patients. The rarity of hiatal hernia suggests that transient lower esophageal sphincter relaxation (TLESR) is the predominant underlying mechanism for GER in patients with NERD.

GASTRO-OESOPHAGEAL REFLUX DISEASE AND BRONCHIAL ASTHMA

The association between gastro-oesophageal reflux and respiratory disease has been appreciated since 1848 when simpson described a patient who died of aspiration pneumonia after an anaesthetic.[42,43]

In 1934 Bray suggested that, in asthmatics, gastric distension due to dietary indiscretion led to reflex mediated bronchoconstriction via vagus nerve.[44]

In 1946 Mendelson called attention to the 'acute asthma-like reaction' following aspiration of liquid gastric contents during induction for anaesthesia.

In 1962 Kenndey described a group of 25 patients with chronic bronchitis, bronchiectasis or pneumonia due to silent gastro oesophagcal reflux.[46,46]

Mansfield and Stein suggested that the vagal nerve might mediate bronchoconstriction in asthmatic patients when stimulated by acid in the oesophagus. This they supplemented the findings by experiments in dogs. Spaulding et al showed in selected control groups using a procedure of acid stimulation that the greatest changes occurred in the Total Airway Resistance in asthmatic patients with positive acid challenge in whom there was an association between attacks of asthma and symptoms of gastroesophageal reflux.[47,48]

MECHANISMS & PATHOPHYSIOLOGY [49-52]

Two basic mechanisms are considered to be responsible for the pulmonary manifestations of gastro-oesophageal reflux. First is the pulmonary aspiration of refluxed gastric contents producing acid induced injury and infection. Second is the neurally mediated reflex bronchoconstriction secondary to irritation of oesophageal mucosa.

ASPIRATION OF REFLUXATE INTO RESPIRATORY SYSTEM

This mechanism could be further elaborated under two subcategories.[53,54]

1. Overt macro aspiration of liquid gastric contents associated with chemical pneumonias and
2. Microaspiration of liquid gastric contents resulting in stimulation of upper airway receptors.

The macroaspiration theory is well documented by the earlier authors as mentioned earlier. However the macroaspiration of gastric contents is not a relatively common association in the patients with bronchial asthma. The response to entry of gastric contents into the lungs depends on the volume of material aspirated, the presence or absence of particulate material and the pH of the aspirate. Aspiration of large quantities of highly acidic material (greater than 1.0ml/kg, pH<2.5) has been shown to cause reflex airway closure associated with hemorrhagic pneumonitis, non cardiac pulmonary oedema and severe hypoxemia. The effect is that of a chemical burn.

Such overt signs of aspiration have rarely been described in association with gastro-ocsophageal reflux in the absence of state in which there is an altered level of consciousness. Because the absence of clinical and radiologic evidence of classic acid aspiration in a proportion of patients with reflux associated pulmonary disorders, alternative explanations have now been hypothesized to explain the pathogenesis.

In recent reviews, the words “micro-aspiration” or “silent aspiration” have begun to appear to explain how gastro-oesophageal reflux could provoke

bronchospasm. The implication of the terms is aspiration limited to the upper airway without progression into the lower respiratory tract. Such a phenomenon has been described by Wynne and associates using experimental solutions of 0.1 ml injected into the oropharynx of mice, noting the physiological changes were limited to the tracheal mucosa and specifically to the surface cell layer.

Microaspiration of gastric contents may be sufficient to stimulate airway receptors to affect respiratory function. Tracheal irritant receptors are believed to be situated in the upper airway epithelium. Tuchmann et al compared the airway responses following tracheal or oesophagcal acidification in the cat and found the tracheal acidification caused significant increase in airway resistance in contrast to the oesophageal acidification. This study supports the view that microaspiration into the trachea is a much more likely mechanism for bronchopasm associated with gastroesophageal reflux than simple acid reflux into the oesophagus.[55]

A number of other studies by Simmonsson et al (1967) using acetic acid aerosol, Larsell O' et al (1974) using acetic acid aerosol and Utell et al (1983)using sulphuric acid acrosol showed to stimulate bronchoconstriction.[57]

Moreover studies in dogs by Sullivan-CE (1979) and Finer et al (1976) have suggested that airway protective mechanisms including cough may be diminished during sleep.

Jolley and co-workers reported that patients with respiratory disorders associated with gastro-oesophageal reflux have an increased frequency of

gastro-oesophageal reflux during sleep as well as symptoms of brochospasm. However Reich et al (1977) and Ghaed and Stein (1979) in their studies to prove this theory could not convincingly demonstrate the microaspiration mechanism by which gastric contents could stimulate bronchospasm.[58]

A third theory that has gained increased popularity because of the inability to convincingly document microaspiration even by sensitive radiolabelled isotopic scintigraphic techniques is that "reflux of gastric contents into the oesophagus alone may stimulate mucosal receptors that are capable of reflexly altering pulmonary mechanics". Indeed studies by Mansfield et al found that acidification of the oesphagus has been shown to increase the total lung resistance in dogs and humans in the presence of oesophagitis.

A variety of oesophageal receptors have been described by vagal unitary recordings including stretch receptors (Andrew 1956), thermoreceptors (EL Quazzani & Mei 1982) and acid sensitive receptors (Harding & Titchen: 1975); The afferent input from such receptors may be capable of reflexly altering control of respiratory timing or bronchial smooth muscle tone. EI. Quazzani and Mei found that stimulation of chemoreceptors in the oesophagus and stomach produced changes in the oesophageal motility and respiratory frequency.

Spaulding et al (1982) performed intra- oesophageal acid perfusion challenge in asthmatic subjects with and without gastro-oesophgeal reflux, non asthmatic subjects with reflux and normal subjects. Spirometric and total

lung resistance were measured before and after infusion. There were no changes in the pulmonary function except in the asthmatic subjects who had a positive acid challenge, changes where mainly in the total lung resistance which significantly increased with reflux and decreased when symptoms where relieved with antacids. The response was even greater in asthmatic subjects who associated reflux symptoms with attacks of asthma.[56]

Davis et al (1983) studied the respiratory response to intraoesphageal acid infusion in asthmatic children during sleep and concluded that during sleep the presence of acid in the lower oesophagus can trigger bronchoconstirction in asthmatic children with a positive Bernstein test and that these children appear to be more susceptible to the bronchoconstrictive effects of intra oesophageal acid at 4 to 5 am than at midnight.[57-60]

Anderson, Schmidt et al (1986) conducted acid infusion study in subjects with oesophagitis but without pulmonary disease, bronchial asthma without oesphagitis and having oesophagitis and asthma. They observed that a modest bronchoconstriction when acid is present in the osophagus is seen in patients with serve asthma and oesophagitis. Atropine inhibits bronchonstricition indicating a vagal mediation.

Herve et al (1986) studied the effect of intra-oesophageal acid perfusion in asthmatic subjects and found that perfusion of acid into the distal oesophagus caused bronchoconstriction in asthmatic subjects with gastro-oesophageal reflux and increased the bronchoconstriction produced by isocapnic hyperventilation and by methacholine in asthmatic subjects without

regard for the presence of gastro-oesophageal reflux.[61,62] Study by Ekstrom et al (1989) concludes that this acid stimulation during daytime in majority of the asthmatic subjects is not a strong and immediate trigger of asthma.[63]

BRONCHOSPASM AS A TRIGGER FOR GASTRO-OESOPHAGEAL REFLUX.

Very little attention has been focused on the possibility that altered respiratory mechanics might cause oesophageal dysfunction. In 1961, Clemencon and Osterman advanced the theory that disturbed intrapleural pressure relationship could predispose to hiatal herria and gastro-oesohageal reflux. Yet no proof has been offered to support this concept.[64,65]

However much attention was paid to the altered diaphragmatic function in this regard. **Transdiaphragmatic pressure is the major force for the gastro-oesophageal reflux**. The observation that asthmatic patients maintain ventilation by increased neuromuscular output during obstruction implies that there is an associated increase in the transdiaphragmatic pressure. Hughs and colleagues speculated that these pressure swings might pump gastric content into the oesophagus.

Most of the previous studies have shown that gastro ocsophageal reflux associated with bronchospasm seem to have increased reflux during sleep. In normal subjects, **transdiaphragmatic pressure swings and phasic diaphragmatic EMG activity increases on falling asleep**, particularly during REM sleep. Tabachink and co-workers observed in asthmatic subjects that during REM sleep there is actually abnormal chest wall movement with

paradoxical inward movement of the ribcage during inspiration. In association there was significant increase in the electrical activity of the diaphragm as well as a considerable increase in the abdominal excursions during inspiration. These findings suggest further augmentation of diaphragmatic contraction in asthmatic patients during REM sleep and thus increasing the gastro-oesophageal reflux by increasing the trans diaphragmatic pressure.

ROLE OF DIAPHRAGM ITSELF IN THE ANTI REFLUX MECHANISM

Intra luminal manometry of the oesophagus has revealed the existence of a high pressure zone at the gastro-ocsophageal junction, characterized by an area of elevated basal pressure and a respiratory induced pressure oscillation that are of greater magnitude than those simultaneously found in the adjacent stomach and oesophagus. Recent human studies indicate that the degree of inspiratory depth contributes significantly to the recorded amplitude of the pressure oscillation. Studies in cat model showed that the respiratory oscillations in this pressure is primarily due to active diaphragmatic contraction during inspiration.

Although diaphragm has been classically considered as being one single functional unit, recent studies also suggest different actions of the **costal and crural** (vertebral) parts of the muscle. They have different embryologic and evolutionary origins in fact the crural part develops in the dorsal mesentery of the oesophagus, which is believed to be responsible for the anti reflux mechanism.

Hyperinflation associated with bronchospasm places the diaphragm at serious disadvantage because of geometrical flattening.

All these factors that cause the alteration in the performance of the diaphragmatic contraction have adverse effect on the anti reflux mechanisms of the diaphragm and, may increase the incidence of gastro-oesophageal reflux in asthmatics.

In recent years investigators have tended to concentrate on the role of drugs used in the treatment of bronchospasm as contributing to the high incidence of gastro-oesophageal reflux seen in these patients. Goyal and Rattan (1973) showed in the opossum that both theophylline and isoproterenol cause a dose dependent relaxation of lower oesophageal sphincter. Berquist and associates found that gastro-esophageal reflux is induced in most normal adults who achieve therapeutic serum levels of theophylline. These studies have led to the concept that high incidence of gastro-oesophageal reflux associated with bronchospasm is drug induced. But these effects of bronchodilators can not be the sole explanation in this regard in clinical studies in which bronchodilator therapy is discontinued before diagnostic evaluation of reflux, the incidence of reflux remains in the range of 25 to 30%. In addition ,in these patients in whom the theophylline therapy is continued during diagnostic evaluation, there is no difference in serum theophylline levels between patients who do or do not have significant reflux.

Sontag and O' connel suggested that most adult asthmatics regardless of the use of bronchodilator therapy have abnormal gastro-oesophageal reflux,

manifested by increased reflux frequency, delayed acid clearance during the day and night and diminished lower oesophageal sphincter pressure. [66]

Moote and coworkers (1968) in their study concluded that during methacholine induced bronchospasm,, subjects with asthma had more episodes of reflux and dropped their pH to lower levels than did the control subjects.[67]

Huberts and colleagues (1988) however failed to demonstrate any adverse effect of a slow release theophylline preparations on gastro-oesophageal reflux in patients with asthma. They further suggested that gastro-oesophageal reflux is not a contraindication to the use of a slow release theophylline in subjects with asthma.[68]

Ekstrom and Tibling (1989) in their study, suggested that mild bronchospasm is unlikely to provoke reflux in patients with asthma and gastro-oesphageal reflux, rather mild bronchospasm is protective against reflux. The reason for this observation could be that the stomach is atonic during stressful events such as acute attack of asthma. Another possible explanation could be that increased abdominal pressure during forced expiration with bronchopasm might squeeze the lower oesophageal sphincter and therefore prevent reflux as long as the lower oesophageal sphincter is located in the abdominal cavity.[69,70]

AIMS AND OBJECTIVES OF THE STUDY

1. To document the various upper gastro-intestinal endoscopic as well as histologic findings of lower oesophagus in patients with bronchial asthma.
2. To estimate the prevalence and magnitude of the reflux associated changes in association with bronchial asthma.
3. To correlate frequency of association with duration of bronchial asthma.
4. To correlate the frequency of association with severity of bronchial Asthma.
5. To document the presence of NERD (Negative Endoscopic Reflux Disease) in patients with bronchial asthma.
6. Endoscopic / histological correlation of oesophagus status in patients with bronchial asthma.

MATERIALS AND METHODS

Thirty patients who were diagnosed to have bronchial asthma and having regular follow up im thoracic medicine out patient clinic were included in the study. From the total mass of patients through questionnaire those who fulfill the selection criteria were selected. The period of study is from February 2008 to September 2009.The materials were obtained from Thoracic Medicine and Medicine Departments.

Selection Criteria

1. Patients who had been diagnosed to have bronchial asthma earlier by history and pulmonary function tests and were on regular follow up.

   Careful history taking was done and the following group of patients were selected for the study.

   1. Patients who do not have satisfactory control of the symptoms in spite of regular treatment.
   2. Patients who experience frequent nocturnal episodes of asthmatic attacks
   3. Patients who have symptoms of gastro-oesphageal reflux disease.

   For these patients , during exacerbation of symptoms, spirometry is performed both before and after bronchodilator administration.A 12% increase (calculated from prebronchodilator values) and a 200ml increase in either FEV1 or FVC defines a positive bronchodilator response and indicates reversibility of obstruction.

Exclusion Criteria

The following group of patients were excluded from the study after clinical examination and investigation because of the confounding factors which will interfere with the results.

1. Patients with systematic Hypertension, Diabetes Mellitus, Chronic real failure, Rheumatological diseases.
2. Patients who have other cardio respiratory disease like pulmonary Tuberculosis, Chronic Obstructive Pulmonary Diseases viz Emphysema, Chronic bronchitis, Bronchiectasis, Coronary atery disease, Congestive Cardiac Failure, Valvular Hear disease etc.
3. Patients with habits of smoking, alcoholism, tobacco ingestion, NSAIDintake.
4. Patients at extremes of age.(<13 & >60)
5. Pregnancy
6. A/c exacerbation of symptoms

The patients were admitted in medical wards and detailed history taking and clinical examination was carried out.

History :

Occupational History

Duration of Illness

Treatment History

Symptomatology : Frequency of attacks

Frequency of nocturnal episodes

Symptoms of attack

Symptoms of reflux disease

(Heart burn, Waterbrash, Chest pain Cough etc)

Factors which precipitate asthmatic episodes

H/O Systematic Hypertension, Diabetes Mellitus, Chronic Renal Failure.

Family History : H/O Atopy and allergy

Drug History : Steroids / B2 Stimulants / Theophylline

Oral / parenteral/ Inhalation Routes

Regular / Irregular

Physical examination:
Cyanosis, comfortable /dyspnoeic , sensorium , Asterixis,presence of action of accessory muscles of respiration

Vital Signs

Pulse rate, regularity, Respiratory rate, Type, Temperature

Systemic Examination

Respiratory system - Chest Shape / symmetry / Measurements / Expansion /Breath sounds and adventitious sounds.

Cardiovascular System - Signs of cardiac failure, Pulmonary Hypertension.

Abdomen

Central Nervous System

Laboratory Investigations

Urine Albumin , Sugar, Blood Counts, Total WBC count, Differential count, RBC counts, Haemoglobin content.

Blood Chemistry

Urea, Creatinine, sugar using standard calorimetric technique. Standard 12 lead electrocardiogram with rhythm strips. X – ray chest postero anterior view.

Pulmonary Function Tests

In this study, **GINA (Global Initiative for Asthma) Classification of Asthma Severity** is used to classify patients.

After establishing the disease and ruling out the exclusion factors the patients were prepared for endoscopy evaluation. A well informed consent explaining the procedure and instructions was obtained patients were instructed to have minimum of 6-8 hours fast during the night prior to endoscopy.

Upper gasto-intestinal endoscopy is carried out in all the patients using PENTEX VIDEO ENDOSCOPY SYSTEM. Prior to procedure the pharynx was anaesthetized using Xylocaine 4% viscous fluid as and when necessary .Intravenous sedation was not necessary.

Endoscopic rapid screening of Upper GI tract and biopsy of lower oesophageal region (3- 4 bits taken). Procedure time is less than 5 minutes. Post procedure : No complications noted.Oxygen cylinder,IV line,Emergency Tray were kept in endoscopy room as backup.

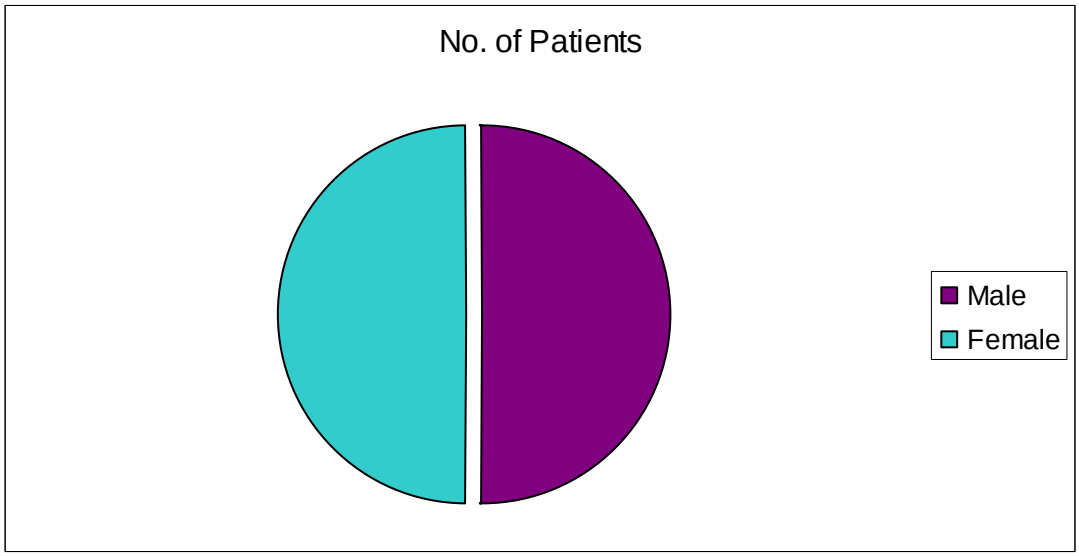
Histological assessment of the samples were done to find out the prevalence of histopathologic changes. Three biopsy samples were taken for each patient from the gastro oesophageal junction.

Basal cell thickness, Length of papillae, and Dysplasia In Situ (DIS) were semiquantitatively scored as 0 (absent), 1 (mild),and 2 (marked) on hematoylin – eosin stained slides obtained from each biopsy site. Basal cell thickness (normal values :<15% at 2 and 4 cm and <20% at the Z – line) and length of papillae (Normal values <50% at 2 and 4 cm and < 66% at the Z – line) were recorded as a percentage of total epithelial thickness.DIS was scored on the basis of their size. In addition, the presence of intraepithelial infiltration of Eosinophils (Score 0 = absent , 1=1 eosinophil, 2 = >1 eosinophil), Neutrophils (0 = absent ,2= present), and Necrosis / Erosions (0 = absent, 2= present) were noted.The presence and number of eosinophils and neutrophils were assessed in the whole sample and the data refer to the mean of the most infiltrated three high power fields.The final histologic "reflux score" resulted from the sum of all above scores for each variable at all biopsy sites. ***The sum of scores of microscopic lesions found in all biopsy sites ranged from 0 to 22 ; a cut – off value (score 2) distinguished efficiently controls from GERD patients.***[71]

RESULTS AND ANALYSIS

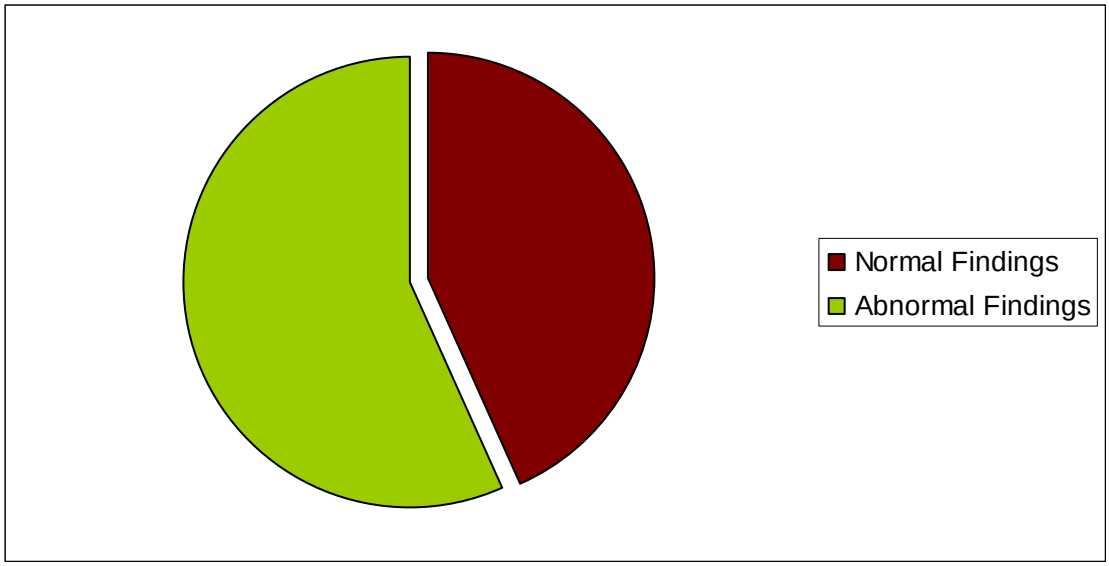
SEX DISTRIBUTION

Out of the 30 patients entered the study 15 were males and 15 were females.



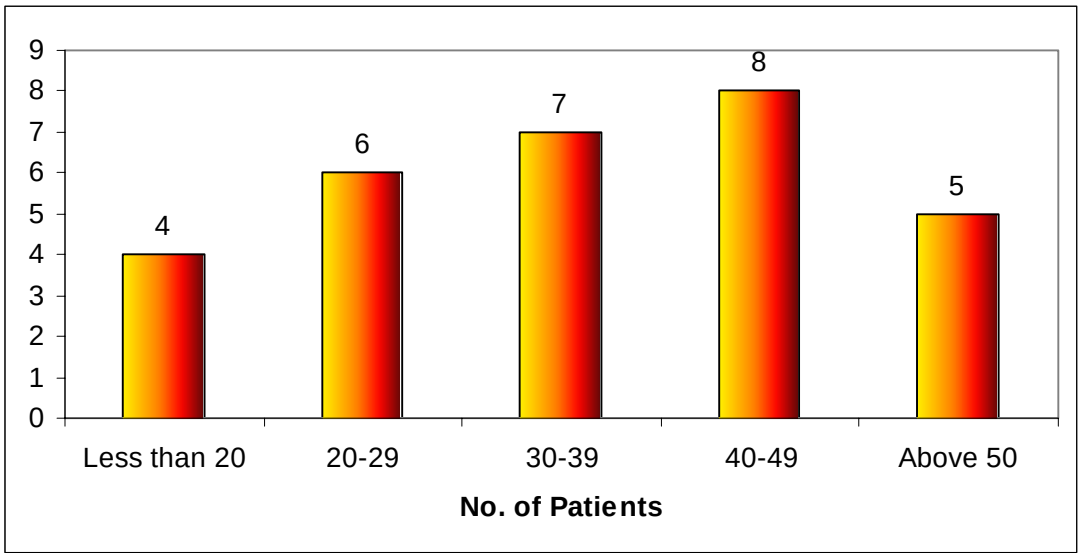
ENDOSCOPY FINDINGS

Out of the 30 patients 17 had various types of abnormal findings.



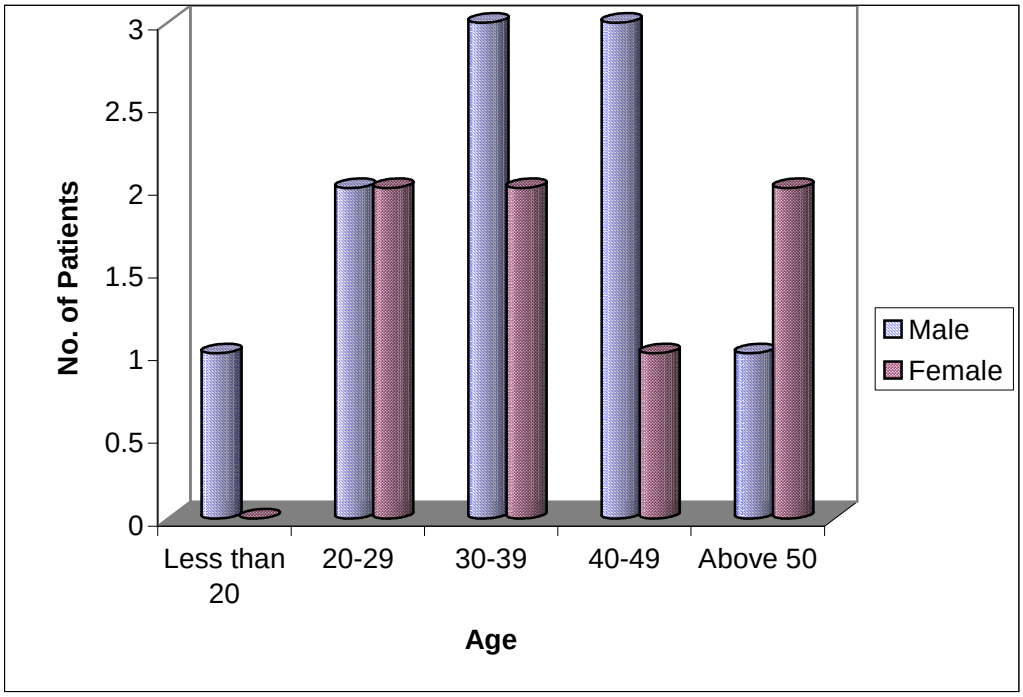
AGE DISTRIBUTION

Sl.No.	Age	No. of Patients
1	Less than 20	4
2	20-29	6
3	30-39	7
4	40-49	8
5	Above 50	5



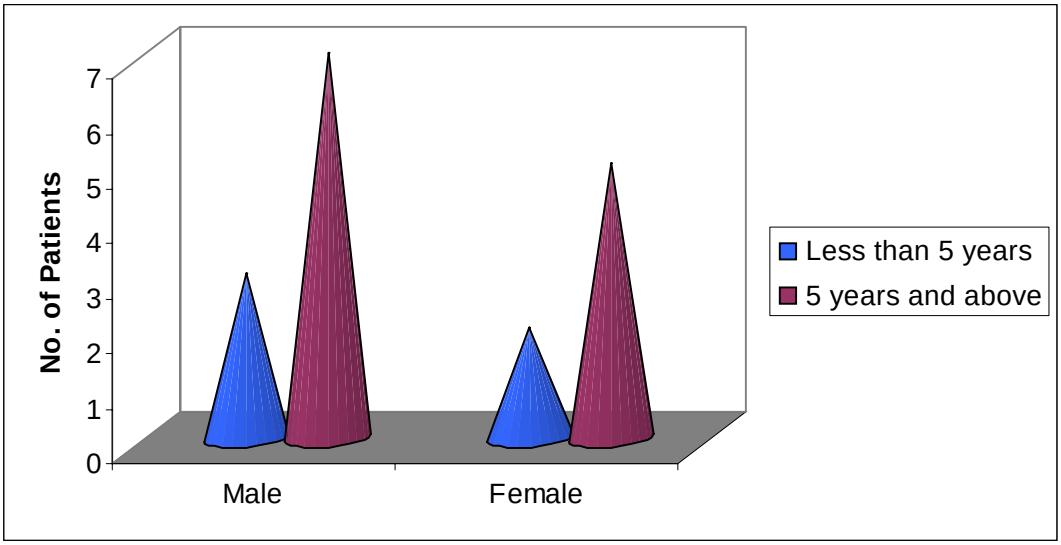
Abnormal Endoscopy findings - Age wise Distribution

Age	Male	Female	Total
Less than 20	1	0	1
20-29	2	2	4
30-39	3	2	5
40-49	3	1	4
Above 50	1	2	3
Total	10	7	17



Abnormal Endoscopy findings relations with duration of illness

Duration of Illness	Male	Female
Less than 5 years	3	2
5 years and above	7	5



INCIDENCE OF ABNORMALITIES

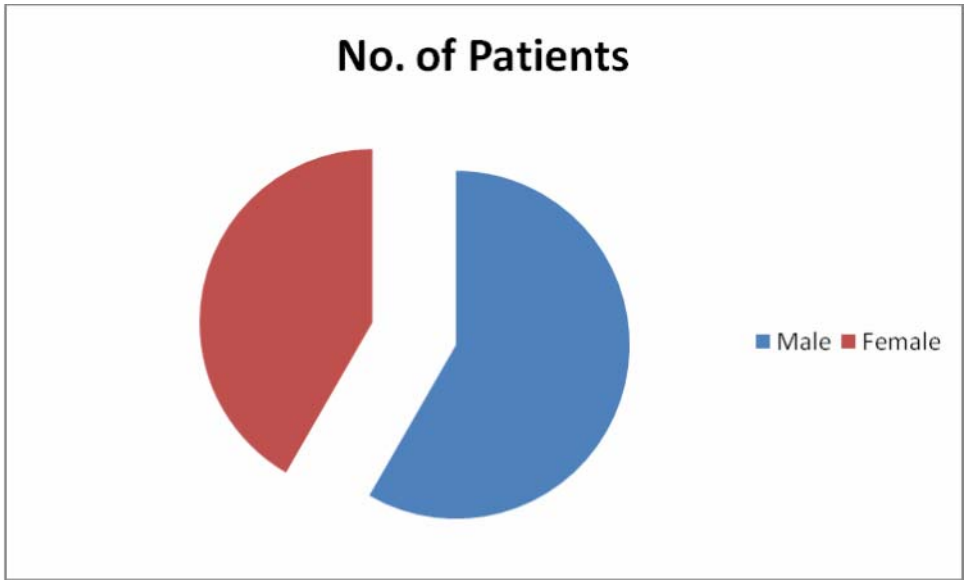
Total No. of Patients – 30

Grade I Oesophagitis	11
Grade II Oesophagitis	1
Grade III Oesophagitis	0
Candidiasis	1
Antral Gastritis	5
Hiatus Hernia	2
Duodenitis	2

REFLUX ESOPHAGITIS – SEX DISTRIBUTION

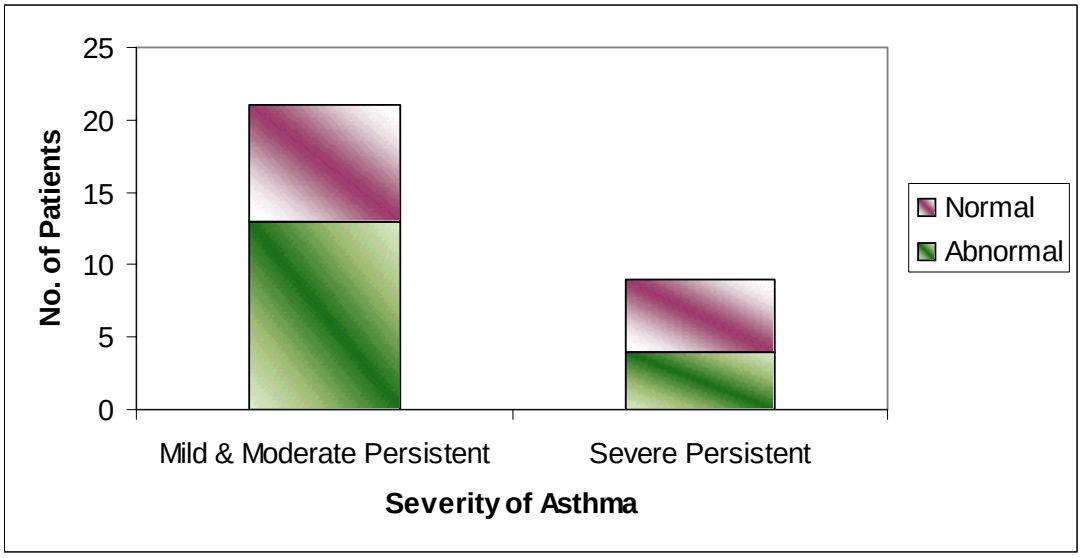
Male -7

Female - 5



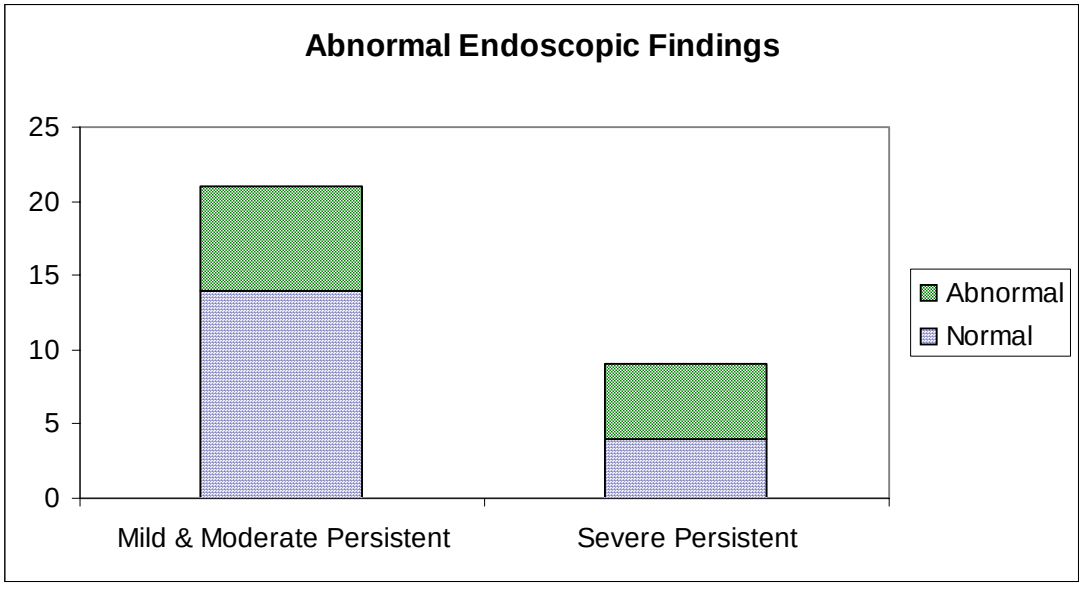
ABNORMAL ENDOSCOPY FINDINGS VS SEVERITY OF ASTHMA

Severity of Asthma	Total Number	Reflux Associated Lesion
Mild & Moderate Persistent	21	13
Severe Persistent	9	4
Total	30	17



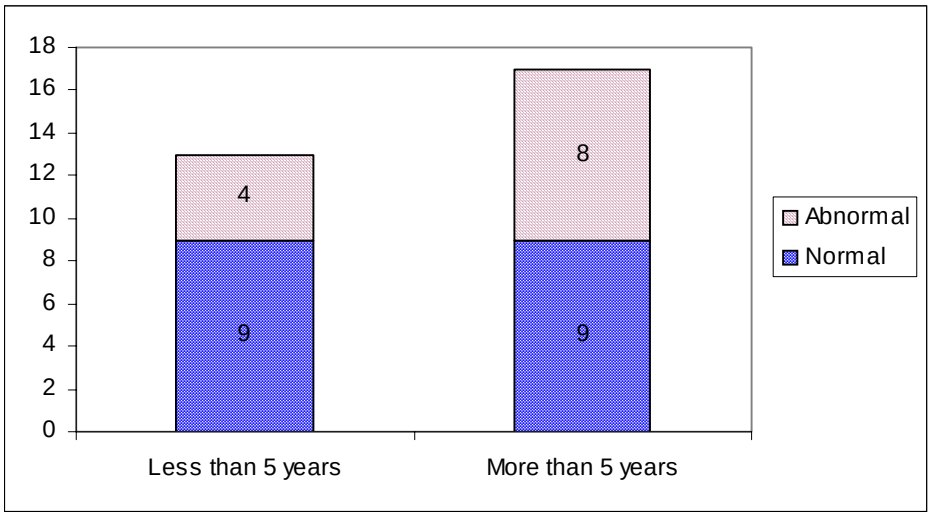
REFLUX ESOPHAGITIS VERSUS SEVERITY OF ASTHMA

Severity of Asthma	Total Number	Reflux Associated Lesion	Percentage
Mild & Moderate Persistent	21	7	33.33%
Severe Persistent	9	5	55.55%



REFLUX ESOPHAGITIS VERSUS DURATION OF ILLNESS

Duration of Asthma	Total Number	Reflux Associated Lesion
Less than 5 years	13	4
More than 5 years	17	8

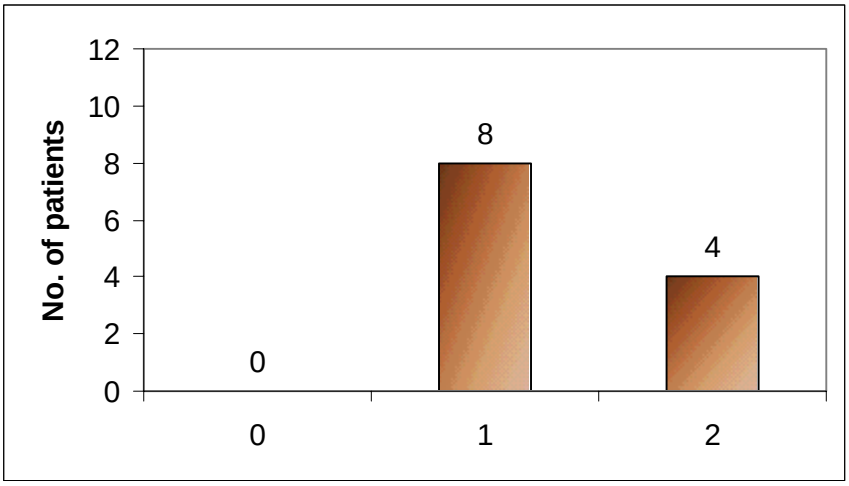


HISTOGICAL CHANGES IN GERD

Findings	**Score**		
	0	1	2
Basal cell thickness	<15% at 2 & 4cm <20% Z-line		
Length of papillae	<50% at 2& 4cm <66% Z-line		
Dysplasia in situ (DIS)			
Neutrophil invasion	Absent	One Neutrophil	>1 Neutrophil
Eosinophil invasion	Absent	One Eosinophil	>1 Eosinophil
Necrosis / Erosions	Absent		Present

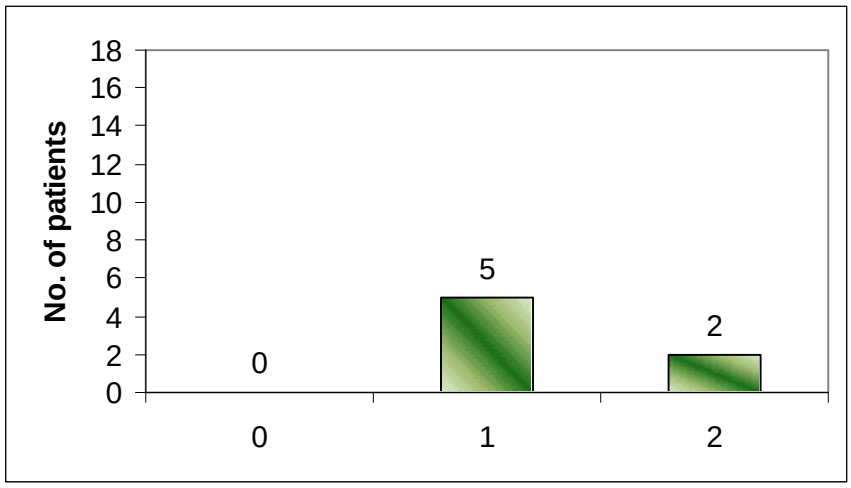
ENDOSCOPY POSITIVITY VERSUS BASAL CELL THICKNESS SCORE

No. of Patients with Positive Endoscopy	Basal Cell Thickness Score	No. of patients
12	0	0
	1	8
	2	4



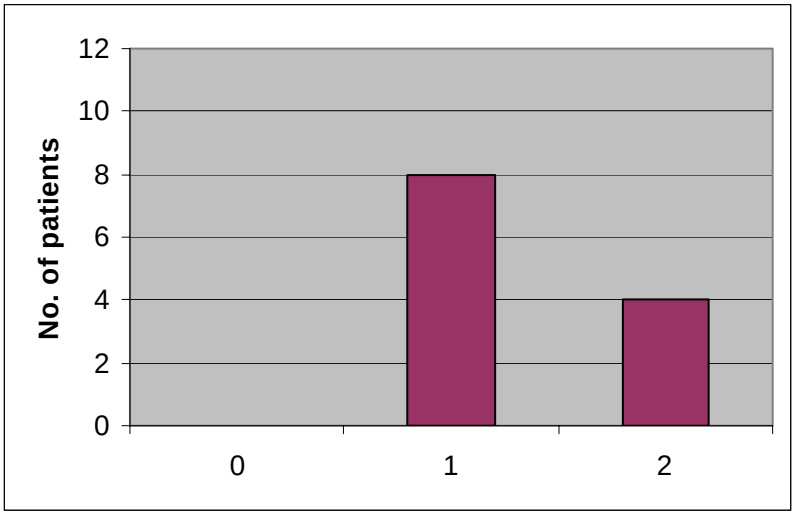
Endoscopy Negativity Versus Basal Cell Thickness Score

No. of Patients with Negative Endoscopy	Basal Cell Thickness Score	No. of patients
18	0	0
	1	5
	2	2



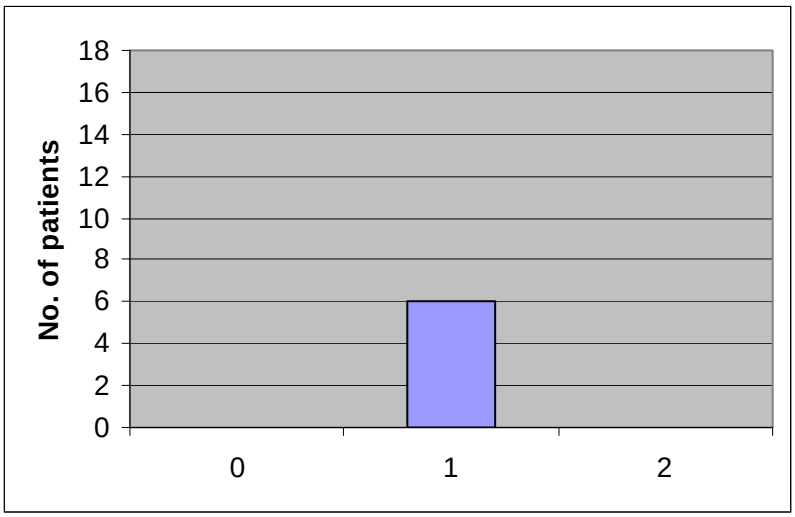
Endoscopy Positivity Versus Length of Papillae

No. of Patients with Positive Endoscopy	Papillary elongation score	No. of patients
12	0	0
	1	8
	2	4



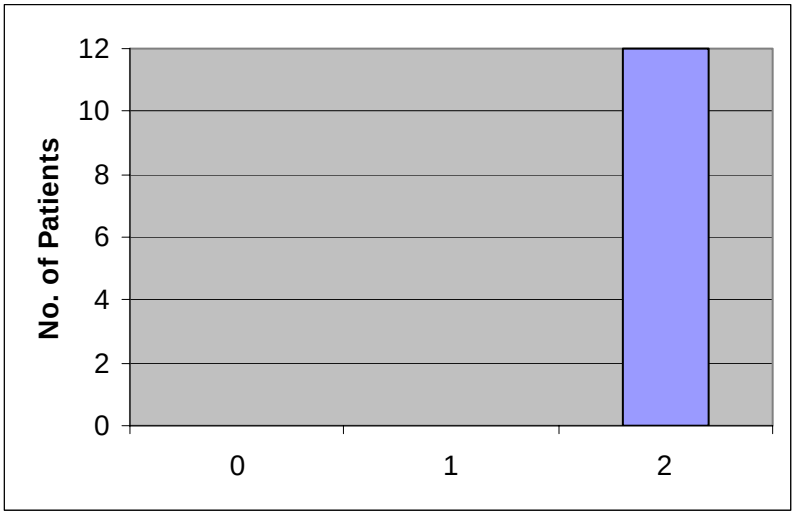
Endoscopy Negativity Versus Papillary Elongation

No. of Patients with Negative Endoscopy	Papillary Elongation Score	No. of patients
18	0	0
	1	6
	2	0



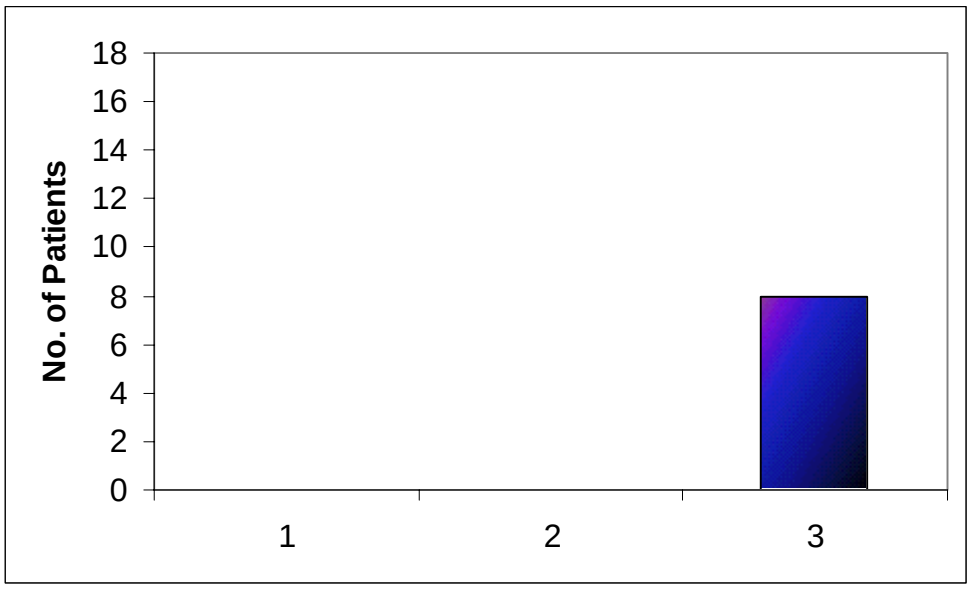
Endoscopy Positivity Versus Eosinophil Invasion

No. of Patients with Positive Endoscopy	Eosinophil Invasion Score	No. of patients
12	0	0
	1	0
	2	12



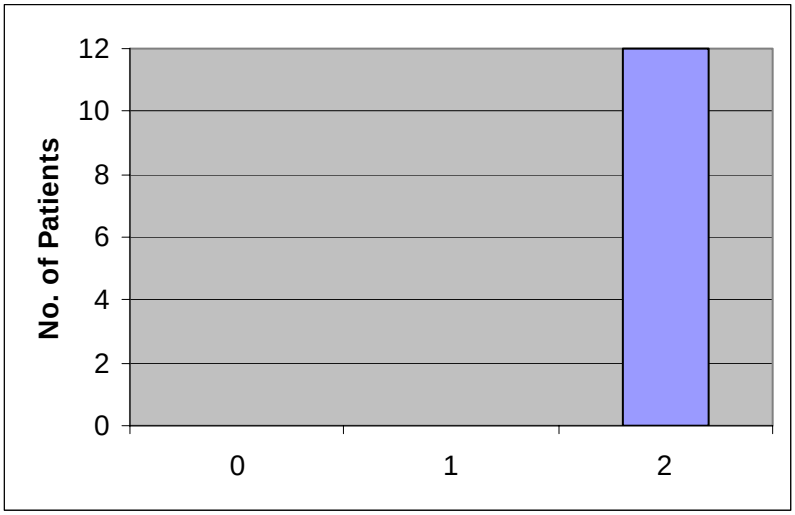
Endoscopy Negativity Versus Eosinophil Invasion

No. of Patients with Negative Endoscopy	Eosinophil Invasion Score	No. of patients
18	0	0
	1	0
	2	8



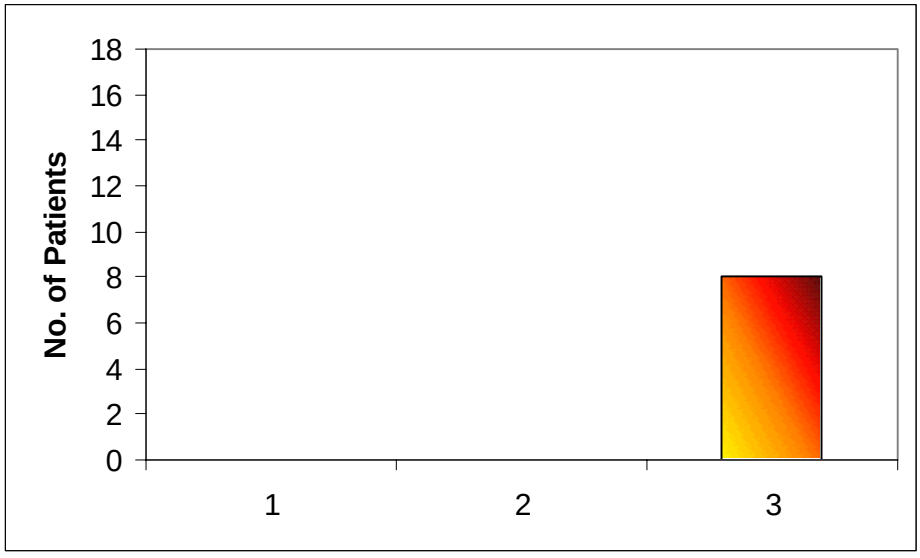
Endoscopy Positivity Versus Neutrophil Invasion

No. of Patients with Positive Endoscopy	Neutrophil Invasion Score	No. of patients
12	0	0
	1	0
	2	12



Endoscopy Negativity Versus Neutrophil Invasion

No. of Patients with Negative Endoscopy	Neutrophil Invasion Score	No. of patients
18	0	0
	1	0
	2	8



Findings	No. of Patients
Endoscopy Positive	12
Histopathology Positive	20
Endoscopy negative	18
Histopathology Negative	10

	Histopathology Positive	Histopathology Negative
Endoscopy Positive	12	0
Endoscopy Negative	8	10

COMPARATIVE ANALYSIS

PREVALENCE OF REFLUX OESOPHAGITIS IN ASTHMATICS

Study	Prevalence
S.J. Sontag et al	39%
Kiljander et al	36%
This Study	40%

Oesophageal Muscosal Status

	Sontag et al.	This Study
Normal (No oesophagitis/No Barrett's)	57.5%	33.33%
Oesophagitis without Barrett's	29.6%	66.67%
Barrett's without Oesophagitis	3.2%	Nil
Barrett's with Oesophagitis	9.7%	Nil

Endoscopic histopathologic Oesophagitis by asthma symptoms and clinical stage – Comparative Analysis

Clinical Stage	Endoscopic Oesophagitis		Histopathologic Oesophagitis	
	Tug et al	This Study	Tug et al	This Study
Mild & Moderate persistent (n=21)	27%	33.3% (n=7)	55%	61.9% (n=13)
Severe Persistent (n=9)	18%	55.5% (n=5)	36%	77.7% (n=7)

	Endoscopic Oesophagitis		Histopathological Oesophagitis	
	Tug et al	This study	Tug et al	This study
Nocturnal attacks + (n=12)	24%	58.3% (n=7)	47%	75% (n=9)
Nocturnal attacks - (n=18)	17%	27.7% (n=5)	35%	61.1% (n=11)

DISCUSSION

Gastro-oesophageal reflux disease is one of the conditions which triggers or worsens the asthmatic condition and hinders with the effective treatment. Physiological reflux, though produces bronchocontriction by reflex vagal stimulation, is not strong enough to produce symptoms of asthma in normal individuals. Acid reflux triggers asthmatic attacks or worsens the symptoms of asthma in the asthmatic patients. This effect is more pronounced if the patients have reflux oesophagitis.

Many authors in earlier studies, proved that the acid application in the lower oesophagus can provoke bronchospasm. They used lower oesophageal contrinuous pH monitoring or oesophageal manometry as the diagnostic tools to evaluate the reflux. But in practical aspect, the reflux disease gets more attention because of its symptoms or complications. In that aspect, upper gastrointestinal endoscopy proves to be an effective diagnostic tool since it enables diagnosis of the reflux associated complications or disorders such as reflux oesphagitis, oesphageal stricture or ulcer, or Barrett's oesophagus or hiatus hernia. Beside direct visualization it allows tissue sampling in doubtful cases.

But documentation of reflux oesophagitis alone is an underestimate of the spectrum of reflux disease, because quite a proportion of patients with symptomatic reflux disease do not have macroscopic evidence of reflux oesphagitis. So negative endoscopy does not entirely rule out the reflux

disease. But it is an important tool, because the therapeutic approach for the reflux disease based upon the endoscopic severity is the best accepted and effective one.

S.J. Sontag, T.G. Schnell and co-workers conducted endoscopic evaluation in a series of asthmatic patients who attended the asthma clinic. All asthmatics had discrete wheezing and either a previous diagnosis of asthma or documented reversible airways obstruction of 20%. The oesphageal mucosa was graded as normal if no erosion or ulcerations were present in the tubular oesophagus, as oesophagitis if a mucosal break with exudates (erosins and / or ulcerations) was present and as Barrett's if specialized (intestinal) columnar epithelium was present. A hiatal hernia was diagnosed if >=2 cm of gastic mucosa appeared above the diaphragm during endoscopy. In their study 39% of the patients with asthma had oesophagitis of Barrett's oesophagus or both. There was no difference in the oesophageal mucosal status between asthmatics who required and those who did not require bronchodilators. 58% of asthmatic had a hiatal hernia. They concluded that oesophagitis is common and independent of the use of bronchodilator therapy in asthmatics.[72]

This study was primarily aimed at finding out the prevalence of reflux associated changes by upper gastrointestinal endoscopy. In the patients attending asthma clinic majority of the patients had moderate to serve persistant asthmatic attacks. They were taking regular bronchodilator medications hence we did not randomize the patients receiving or not receiving bronshodilators.

Since reflux oesophagitis is one of the conditions which hinders with effective asthma treatment, we selected the cases who do not have adequate control of asthma in this study. Thorough questionnaire was put to evaluate the gastrointestinal symptoms.

We also eliminated the patients who had confounding factors such as chronic obstructive airways disease, smoking, alcoholism, tobacco ingestion. NSAID intake, pregnancy, Diabetes mellitus, chronic renal failure because these conditions will affect the oesophageal motility and lower oesophageal sphineter tone so they possibly tend to produce oesophagitis and other endoscopic changes.

Sontag et al reported a prevalence of 39% of oesophagitis and / or Barrett's oesophagus in their study of asthmatic patients.. In this study of 30 patients, 7 males and 5 females had reflux oesophagiti. (23.3% and 16.67% respectively). Comprising a total of 40% of oesophagitis in this study.

Out of the 30 patients. 15were male (50%) and 15were female (50%). The mean age of male was 42.27 years ranging from 13 to 68 years. The mean age of female was 36.79 years ranging from 16 to 60 years. The mean duration of asthma was 7.95 years in male and 5.18 years in females.

ENDOSCOPIC LESIONS

Reflux Oesophagitis

Of the 30 patients studied 17 had abnormal endosopy findings thus comprising of 56.67%of abnormal findings in this study. Out of the 15 males

studied 10 had abnormal findings (66.67 %) and out of the 15 females, 7 had abnormal finding (46.67%). This male prepondance of lesions could not be explained by the disease per se alone but other factors like strenuous work ,tea or coffee ingestion could also play a role.

Of the endosocpic findings reflux associated findings were worth the comment. Reflux oesophagitis was found in 12 patients (40%) and pulled up gastro-oesophageal junction consistent with hiatus hernia was found in 2 patients (6.67%).Of the twelve patients 11 patients had Grade 1 oesophagitis and one patient had grade II oesophagitis. . However, we adopted the savary miller scale of classification of oesophagitis but the original study by Sontag adopted the Hetzel classification in which small erythemas are included as grade I lesions. In our criteria small erythemas are not included as evidence of oesophagitis .Erosions, and multiple erythemata are only graded as grade 1 oesophagitis.

Studies by Indian authors Agarwal et al also reported similar range of prevalence of reflux oesophagitis in asthmatic patients.

HISTOPATHOLOGICAL FINDINGS

In this study, we included the histopathological correlation of reflux oesophagitis . Histopathological changes consistent with GERD were present in all the 12 patients with reflux oesophagitis.

Out of the 18 patients who were endoscopically negative for reflux oesophagitis , 8 had findings consistent with GERD. (5 male : 3 female) (44.4%).

Tug et al conducted a study on the association between severity and stage of asthma symptoms in a distinctive period and gastrooesophageal reflux. In this study they correlated endoscopic –histopathologic oesophagitis by asthma symptoms and clinical stage. They reported the prevalence of Endoscopic oesophagitis to be 27% and histopathologic oesophagitis to be 55% in patients with mild-intermittent / persistent asthma. In moderate persistent asthma, the prevalence was 18% and 36% respectively.They also correlated the frequency of GER symptoms and endoscopic – histopathologic oesophagitis in patients with and without nocturnal symptoms. Histopathological diagnosis was based on the definition given by Ismail – Beigi et al.[73]

In this study, the prevalence of Endoscopic oesophagitis is 33.3% (n=7) and histopathological oesophagitis is 61.9%(n=13) in patients with mild and moderate persistent asthma.

In patients with severe asthma, the endoscopic prevalence is 55.5% (n=5)and histopathologic prevalence is 77.7%(n=7).

The prevalence of Endoscopic oesophagitis and Histopathologic oesophagitis in patients with nocturnal attacks were 58.3%(n=7) and & 75%(n=9) respectively, In patients without nocturnal attacks the prevalence is 27.7% (n=5) and 61.1%(n=11) respectively.The prevalence of both

endoscopic and histopathological reflux is higher in patients with nocturnal symptoms.But these values are higher compared to study by Tug et al.

Similarly Kiljander et al conducted a study about the prevalence of GERD in adult asthmatics in which they used 24 hour pH metry as the standard. The prevalence of reflux oesophagitis in their study was 36%.[74]

Reflux oesophagitis is the sequelac and indicator of long standing and moderate to severe gasto-oestophageal reflux. It is more severe at the squamo-columnar junction. It can extend upwards to many centimeters, but visible changes are usually confined to the distal 5 cm. Grading the extent of the macroscopic reflux oesophagitis is of great importance as it is the best measure of severity and the best predictor of outcome with treatment. In our study we did not try to establish the cause effective mechanisms of reflux and asthma.We screened the patients with intractable asthma for the presence of reflux oesophagitis ,thus it would be beneficial to the patients to start anti – reflux treatment in them.Many published reports favour the point that effective anti – reflux medical and surgical management will reduce the severity of asthma and reflux associated bronchospasm .

There is significant difference present in the prevalence of reflux esophagitis between males and females.Out of the 15 males 7 had reflux oesophagitis (46.67%) whereas in females 5 out of 15 had reflux oesophagitis(33.33%).

The prevalence of reflux oesophagitis is higher in long standing and severe asthmatics.In this study reflux oesophagitis was present in 23.33% of patients with less than 5 years of disease and 33.3% of patients with 5 years or more of disease duration.Similarly out of the 21 patients with mild and moderate persistent asthma 33.33% (n=7) had reflux oesophagitis whereas out of the 9 patients with severe persistent asthma 55.55% (n =5) had reflux oesophagitis.

Thus this study clearly indicates that reflux oesophagitis is a common association in bronchial asthma patients with long standing and / or severe degree of disease.

In our study the prevalence of NERD (Negative Endoscopic Reflux Disease) is 44.44%. which is statistically significant.

OTHER LESIONS:

Hiatus hernia as described by authors .ie, presence of > 2cm of gastric mucosa appearing above the diaphgram during endoscopy was present in only 2 patients (6.67%) in this study.Out of these , one patient had reflux oesophagitis.But the western literature quotes the presence of hiatus hernia to the tune of upto 45% in various series.

Oesophageal candidiasis was present in only one patient which was stastically insignificant . After ruling out other possibilities, the only trigger which could be blamed was the oral steroid intake.

5 of the 30 patients had Antral gastritis (Male 3 : Female 2) had antral erosions and gastritis and two male patients had gastric ulcer (6.67%).Duodenitis was present in 3 cases (2females and one male).These disorders could be explained by the hyperacidity by the stress due to the disease or steroid intake.

CONCLUSIONS

Following are the conclusions drawn in the study of 30 cases of bronchial asthma for upper gastrointestinal endoscopic changes.

- Out of the 30 patients ,15 were males and 15 were females
- Out of the 30 patients ,17 had abnormal endoscopy findings (56.67%)
- Out of the 15 males studied ,10 had abnormal findings (66.67%)
- Out of the 15 females studied , 7 had abnormal findings (46.67%)
- There is a slightly higher prevalence of abnormal endoscopy findings in males with a ratio of 1.43:1
- Abnormal endoscopy findings were not well correlated with the age group of the patients.But it has correlation with the duration of the illness
- Out of the 13 patients with disease duration less than 5 years ,5 had abnormal findings (38.46%), where as out of the 17 patients with disease duration more than 5 years , 12 had abnormal findings (70.5%)
- Among abnormal findings ,reflux oesophagitis stands first with prevalence of 40% (n = 12) among which Grade I oesophagitis is 36.67% (n=11) and Grade II is 3.3% (n=1)
- Reflux oesophagitis was slightly more prevalent in males than in females with a ratio of 1. 4:1

- Out of the 15 males ,7 had reflux oesophagitis (46.67%) & out of the 15 females 5 had reflux oesophagitis (33-33%)
- Pulled up gastro oesophageal junction consistent with hiatus hernia was found in 2 patients (6.67%).Out of this one had reflux oesophagitis.
- Prevalence of reflux oesophagitis was slightly higher in longstanding asthmatics.Out of the 13 patients with disease duration less than 5 years 4 had reflux oesophagitis (30.8%).Out of the 17 patients with disease duration more than 5 years, 8 had reflux oesophagitis (41.!8%)
- Reflux oesophagitis was slightly more prevalent in diseases of severe degree.Out of the 21 patients with mild and moderate persistent asthma, 7 had reflux oesophagitis (33.33%);where as out of the 9 patients with severe persistent asthma , 5 had reflux oesophagitis (55.55%)
- Histopathological findings consistent with GERD were present in all the patients with reflux oesophagitis.
- Out of the 18 patients who do not had reflux oesophagitis(NERD),8 patients had histopathological findings consistent with GERD (44.44%) (NERD – higher percentage in this study).
- In patients with mild and moderate persistent asthma, the prevalence of endoscopic esophagitis is 33.3%(n=7) and histopathologic oesophagitis is 61.9%(n=13).

- In patients with severe persistent asthma, the prevalence of endoscopic oesophagitis is 55.5% (n=5) and histopathologic oesophagitis is 77.7%(n=7)
- In patients with nocturnal attacks,the prevalence of endoscopic oesophagitis is 58.3%(n=7) and histopathological oesophagitis is 75%(n=9).
- In patients without nocturnal attacks,the prevalence is 27.7%(n=5) and 61.1% (n=11) respectively.
- Total prevalence of reflux oesophagitis (Endoscopy And Histology wise) is 66.67% (n=20)

SUMMARY

The finding that prevalence of Reflux oesophagitis is more common in asthmatics reconfirmed in this study.

Reflux oesophagitis is present in significant proportion of bronchial asthma patients of long standing illness and more severe disease pattern. Since presence of reflux oesophagitis worsens the disease pattern and hinders with effective control , these patients do not have satisfactory control of their asthma symptoms.

This study established the Importance of histology in negative endoscopic reflux. Significant number of patients with negative endoscopy had histopathological evidence of oesophagitis, thereby proving the role of biopsy in GERD.

Antireflux therapy with proton pump inhibitors and prokinetics may provide symptomatic improvement in these patients which is beyond the scope of this study.

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STUDY ON UPPER GI ENDOSCOPY

FINDINGS IN PATIENTS WITH BRONCHIAL ASTHMA

PROFORMA

NAME : AGE : SEX : IP/OP NO :

OCCUPATION : DURATION OF ILLNESS:

TREATMENT : REGULAR / IRREGULAR

HT : WT : BMI :

SYMPTOMS :

BREATHLESSNESS

WHEEZE

COUGH

SPUTUM

NOCTURNAL EXACERBATION

SYMPTOM FREE INTERVAL

GI SYMPTOMS

HEART BURNS

BELCHING

NAUSEA / VOMITING

POST CIBAL BLOATING

STICKINESS IN THROAT

WATER INTAKE FOR EASY SWALLOWING

SIGNS

DYSPHAGIA

COMFORTABLE / DYSPNOEIC

CYANOSIS

ASTERIXIS

VOICE CHANGES

SUPINE POSTURE DIFFICULTIES

CVS :

RS :

ABDOMEN :

CNS :

TRIGGERS :

UPPER RESPIRATORY INFECTION

EXERCISE

COLD AIR

SMOKING

POLLENS/DUST

DRUGS

EMOTIONAL UPSET

OTHERS

OTHER HISTORY

HYPERTENSION

PULMONARY TB

CAHD

H/O ATOPY & ALLERGY

FAMILY H/O ASTHMA

FAMILY H/O ALLERGY

SMOKING

ALCOHOLISM

OTHERS

DRUGS

STEROIDS : ORAL /INHALER /IV

XANTHINES

BETA – 2 AGONISTS

OTHERS

INVESTIGATIONS

Hb : TC : DC:

RBC :

URINE COMPLETE :

ECG :

CHEST X-RAY

USG ABDOMEN

PULMONARY FUNCTION TESTS:

STUDY ON UPPER GI ENDOSCOPY

FINDINGS IN PATIENTS WITH BRONCHIAL ASTHMA

PROFORMA

NAME

AGE

SEX

DURATION OF BRONCHIAL ASTHMA

OG JUNCTION LENGTH

GERD : + / -

LAX OGD : YES/NO

ESOPHAGITIS : YES/NO

STAGE I/A :

STAGE 11/B :

STAGE 111/C :

STAGE 1V/D :

STOMACH

FUNDUS

BODY

ANTRUM

DUODENUM

FIRST PART

SECOND PART

NERD :

BIOPSY : YES /NO

SITE OF BIOPSY :

BRONCHIAL ASTHMA

ESOPHAGITIS : Yes / No

If Yes, Grade :

BIOPSY : Yes / No

If Yes, Findings:

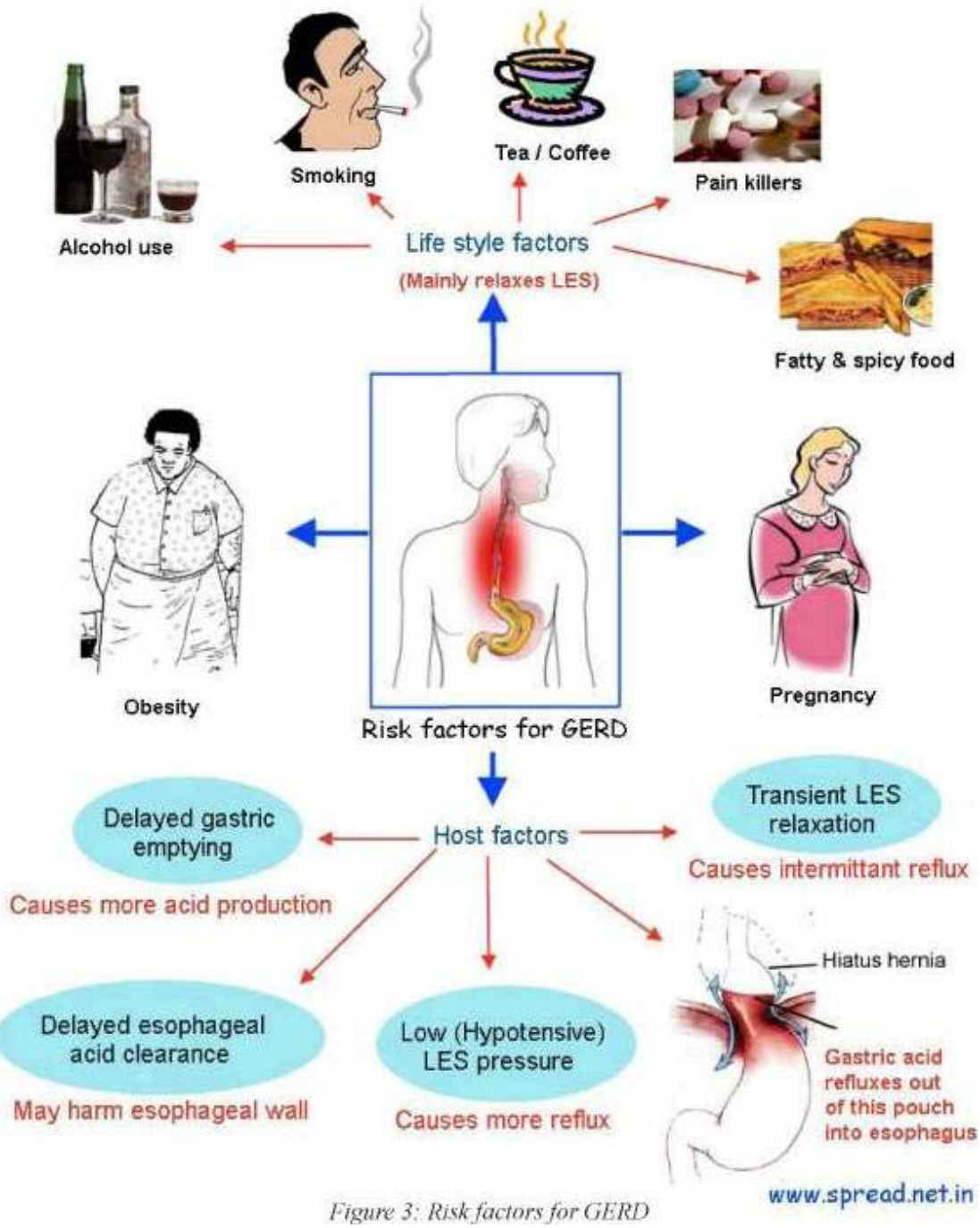
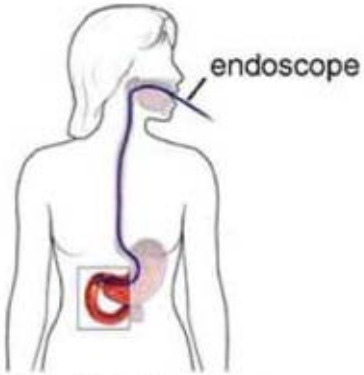
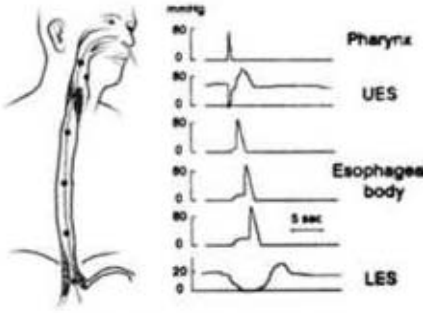


Figure 3: Risk factors for GERD



Upper GI endoscopy

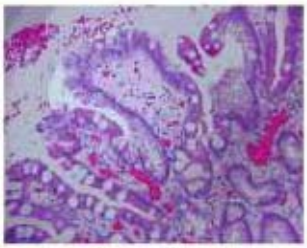
First measure to diagnose suspected GERD



Esophageal manometry

For studying esophageal body motility & LES

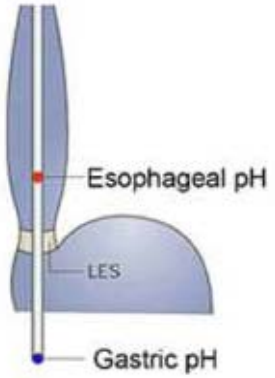
Diagnosis of GERD



Histopathological assessment of esophageal biopsy

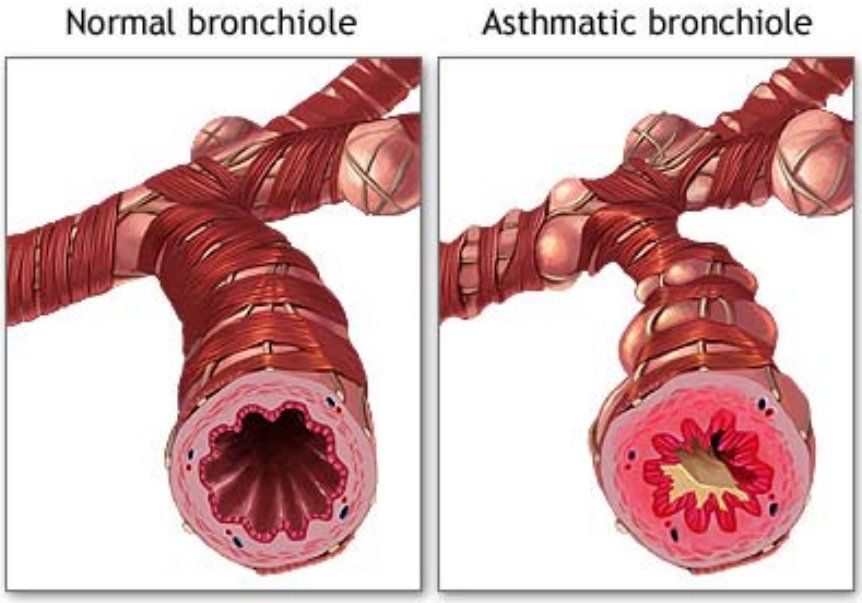
Barium swallow

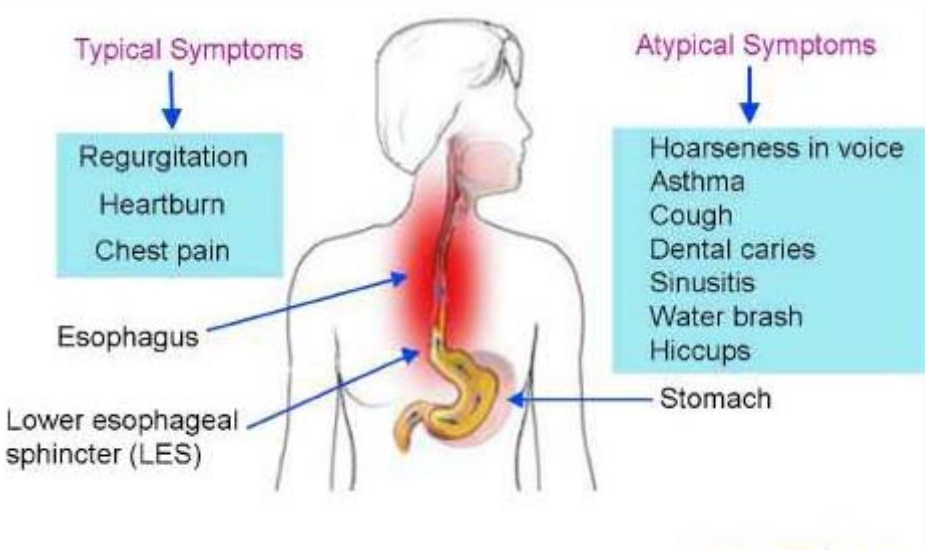
For diagnosis of complicated GERD

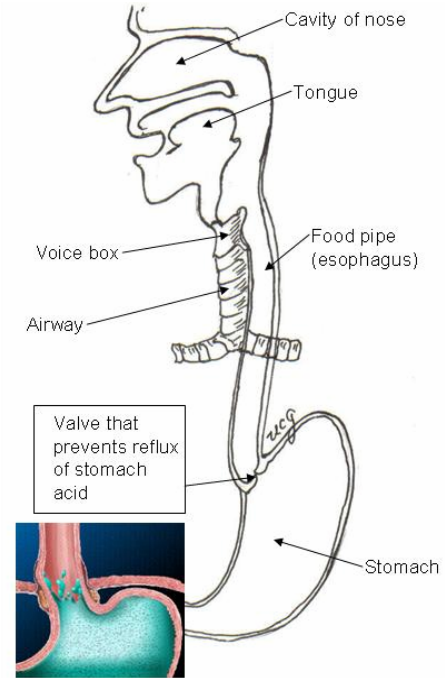


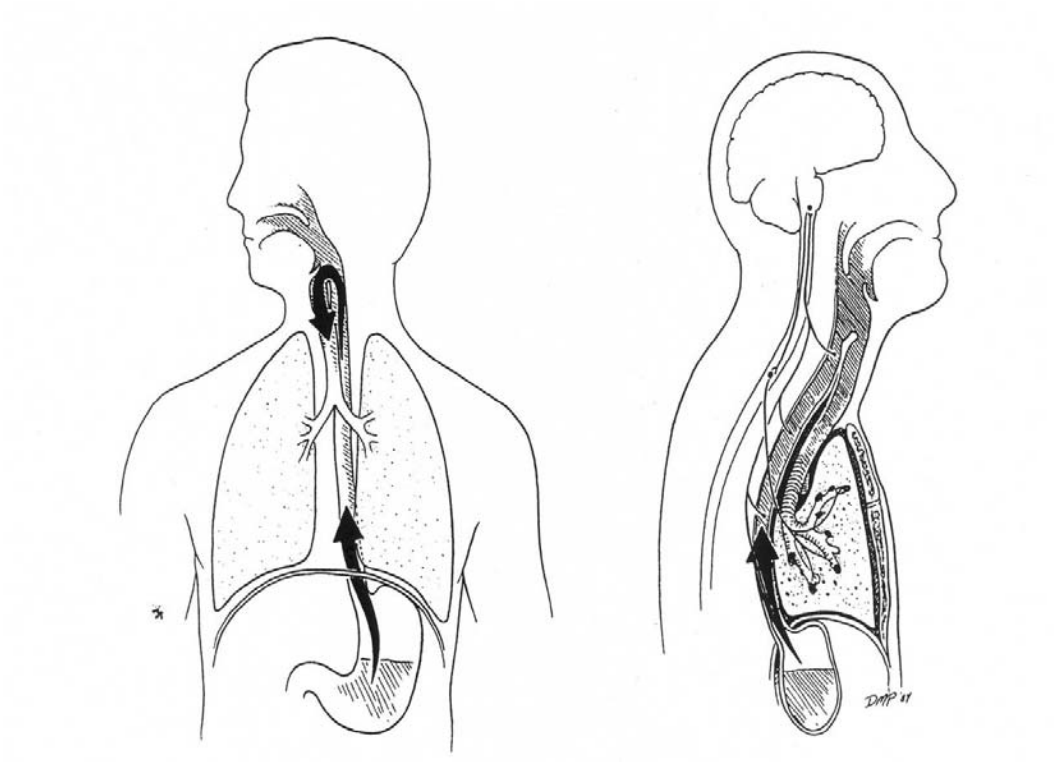
24-h pH metry

For diagnosis of esophageal acid exposure


Normal bronchiole
Asthmatic bronchiole


Typical Symptoms
Regurgitation
Heartburn
Chest pain
Esophagus
Lower esophageal sphincter (LES)
Atypical Symptoms
Hoarseness in voice
Asthma
Cough
Dental caries
Sinusitis
Water brash
Hiccups
Stomach


Cavity of nose
Tongue
Voice box
Food pipe
(esophagus)
Airway
Valve that
prevents reflux
of stomach
acid
Stomach



MECHANISM OF EXTRA OESOPHAGEAL GERD

MASTER CHART

Sl. No.	Age (yrs.)	Sex	Duration of Asthma (Yrs.)	Symptom Frequency	Nocturnal Symptoms	Upper GI Endoscopy findings	HISTOPATHOLOGICAL FINDINGS					
							BCT	Length of Papillae	Eosinophil inuasion	Neutrophil inuasion	Necrosis/Erosin	DIS
1	47	M	6	2/Wk	1/Wk	Gr.I RE, antral gastritis	2	2	2	2	0	0
2	21	M	4	2-3/Wk	Nil	Hiatus hernia						
3	31	M	5	1-2/Wk	Nil		1	1	2	2	0	0
4	45	F	7	1-2/Wk	Nil	Gr.I RE	2	2	2	2	0	0
5	16	M	3	2-3/Wk	Nil							
6	48	F	7	Daily	3-4/Wk							
7	55	M	8	Daily	3-4/Wk	Gr.I RE	2	2	2	2	0	0
8	52	M	6	2-3/Wk	Nil		1	1	2	2	0	0
9	34	M	6	1/Wk	2-3/Wk	Gr.I RE, antral gastritis	2	2	2	2	0	0
10	27	F	3	1-2/Wk	Nil	Gr.I RE, antral gastritis	2	2	2	2	0	0

Sl. No.	Age (yrs.)	Sex	Duration of Asthma (Yrs.)	Symptom Frequency	Nocturnal Symptoms	Upper GI Endoscopy findings	HISTOPATHOLOGICAL FINDINGS					
							BCT	Length of Papillae	Eosinophil inuasion	Neutrophil inuasion	Necrosis/Erosin	DIS
11	60	F	7	Daily	2-3/Wk	Gr.I RE	2	2	2	2	0	0
12	65	F	8	Daily	3-4/Wk	Gr.I RE	2	2	2	2	0	0
13	38	F	6	2/Wk	Nil	Gr.I RE	2	2	2	2		
14	53	F	6	2/Wk	Nil		1	1	2	2		
15	49	F	7	1/Wk	Nil							
16	32	F	4	1-2/Wk	Nil							
17	40	M	9	Daily	3-4/Wk	Gr.II RE, Candidiasis	2	2	2	2	0	0
18	40	F	10	Daily	3-4/Wk		1	1	2	2		
19	35	M	2	2-3/Wk	Nil	Duodenitis, Gr.I RE	2	2	2	2	0	0
20	20	F	2	1-2/Wk	Nil	Duodenitis						
21	38	F	4	1-2/Wk	Nil	Antral gastritis						

Sl. No.	Age (yrs.)	Sex	Duration of Asthma (Yrs.)	Symptom Frequency	Nocturnal Symptoms	Upper GI Endoscopy findings	HISTOPATHOLOGICAL FINDINGS					
							BCT	Length of Papillae	Eosinophil inuasion	Neutrophil inuasion	Necrosis/Erosin	DIS
22	41	M	8	Daily	3-4/Wk	Gr.I RE, antral gastritis	2	2	2	2	0	0
23	13	M	2	2/Wk	2/Wk							
24	40	F	7	Daily	2-3/Wk		1	1	2	2		
25	14	F	3	1-2/Wk	Nil							
26	16	M	3	2-3/Wk	Nil	Hiatus hernia						
27	29	M	6	2-3/Wk	Nil	Gr.I RE	2	2	2	2	0	0
28	29	M	6	2-3/Wk	Nil		1	0	2	2		
29	35	F	3	Daily	2-3/Wk		1	1	2	2	0	0
30	25	M	2	1-2/Wk	Nil		0	0	2	2		